University of Sussex

Investigation of Novel Thermal Cyclisation Reactions

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Declaration

I hereby declare that this thesis has not been and will not be submitted in whole or in part to another University for the award of any other degree.

Signature:

Date:

Dedication

Dedicated to my family

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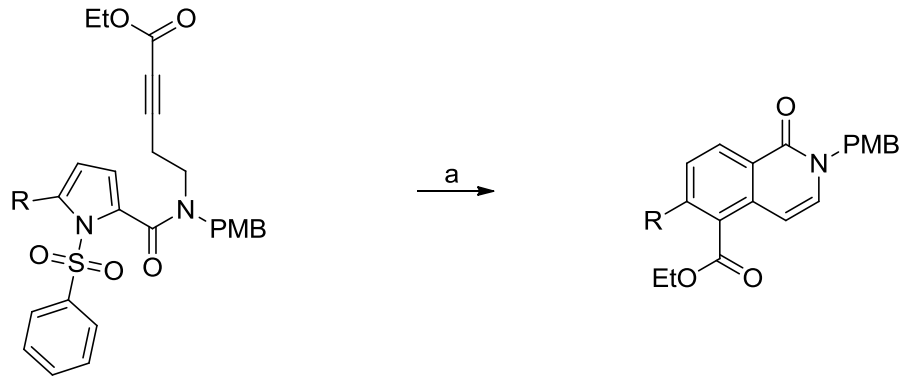
Abstract

Part 1. Concise Synthesis of Highly Substituted Isoquinolin-1(*2H*)-ones *via* IMDA

The primary goal of this DPhil research project was to further investigate the mechanism of a novel thermally activated cyclisation reaction discovered within the Parsons' research group. Through the synthesis and cyclisation of the substituted pyrrole rings **2.38a-c** we have investigated the mechanism and increased the scope of the cyclisation reaction.



2.38a-c **2.39a-c**

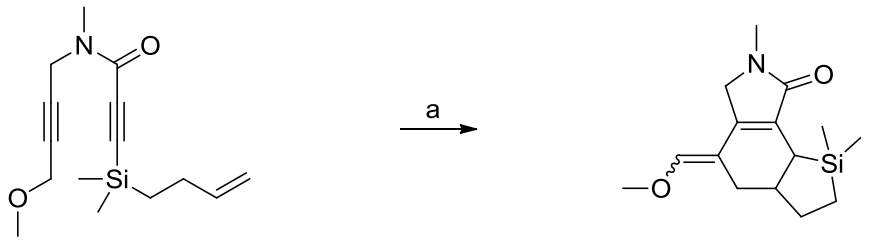
2.38a: R = Et, **2.38b**: R = *n*-Bu, **2.38c**: R = *i*-Bu

Reagents and Conditions: (a) Pyridine, LiI, reflux.

We have also developed a robust route to advanced intermediate **2.10** in the synthesis of hymenialdisine **2.1**.

Part 2. Investigation and Development of a Novel Cascade Reaction

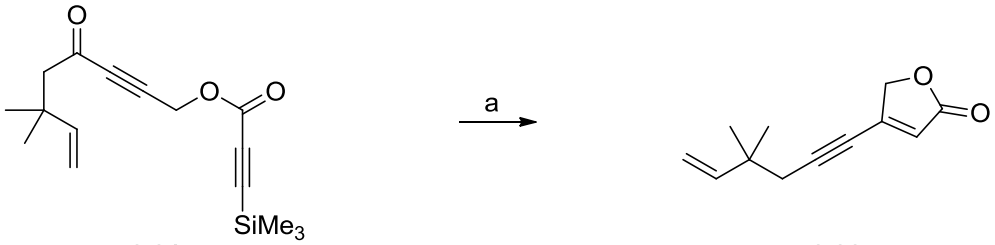
The aim of this DPhil research project was to devise and execute a series of experiments to gain a better mechanistic understanding of the novel thermal cyclisation, discovered within the Parsons' research group. To further investigate the mechanism and scope of the cyclisation, the model system **2.1** was initially selected.



2.1 **2.2**

Reagents and Conditions: (a) Toluene, reflux, 0.01M, 38%.

Through extensive modification and manipulation of the cyclisation precursor **2.1**, we have increased the scope of the cyclisation and postulated a reaction pathway. During these studies remarkable transformation of ketone **2.81** to alkyne **2.82** was also observed.



2.81 **2.82**

Reagents and Conditions: (a) Toluene, 0.01M, reflux, 6h, 30%.

The repeatability of the above reactions was also investigated by synthesising various analogues.

Abbreviations

Å	Ångstrom
Ac	acetyl
AcOH	acetic acid
AIBN	azobisisobutyronitrile
AN	acceptor number
aq.	aqueous
Ar	aromatic
BC	Bergman cyclisation
Bn	benzyl
Boc	*tert*-butoxycarbonyl
b.p.	boiling point
Bu	butyl
t-Bu	*tert*-butyl
n-Bu	butyl
n-BuLi	butyllithium
Bz	benzoyl
°C	degrees Celsius
cat.	catalytic
CDI	1,1’-carbonyldiimidazole
conc.	concentrated
cy	cyclohexyl
D	deuterium

D-A	Diels-Alder
DCC	1,3-dicyclohexylcarbodimide
DCE	1,2-dichloroethene
DCM	dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulphide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
E*a*	activation energy
EDCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI+	electron impact
EPR	electron paramagnetic resonance
Et	ethyl
eq.	equivalents
FMO	Frontier Molecular Orbital
g	gram(s)
h	hour(s)
HBTU	*O*-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate
HOMO	highest occupied molecular orbital
HOBt	*N*-hydroxybenzotriazole
HRMS	high resolution mass spectrum

Hz	Hertz
IEDDA	inverse electron demand Diels-Alder
IMDA	intramolecular Diels-Alder
IR	infrared spectroscopy
IRC	intrinsic reaction coordinate
J	coupling constants
kDa	Daltons
LED	light-emitting diode
LDA	lithium di-*iso*-propylamide
LUMO	lowest unoccupied molecular orbital
M	molar
Me	methyl
MeI	methyl iodide
MeLi	methyllithium
MeOH	methanol
min.	minute(s)
mL	millilitre
mol	mole
mmol	millimole
MOM	methoxy methyl
m.p.	melting point
Ms	methanesulfonyl
M.S.	molecular sieve
MS	mass spectrometry
MRSA	methicillin-resistant staphylococcus aureus

MW	microwave
NDA	normal electron demand Diels-Alder
NMR	nuclear magnetic resonance
Nu^-	nucleophile
p	para
P	protecting group
Ph	phenyl
PMB	*para*-methoxy benzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
i-Pr	isopropyl
i-PrOH	isopropyl alcohol
pTSA	*para*-toluenesulfonic acid
rt	room temperature
SM	starting material
SOI	secondary orbital interaction
TADA	transannular Diels-Alder
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl triflate
TDP	photodynamic therapy
TES	triethylsilyl
tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSOH	trimethylsilanol
Tol.	toluene
TS	transition state
Ts	tosyl
TsOH	4-methylbenzenesulfonic acid
THP	tetrahydropyran
UV	ultraviolet
W-H	Woodward-Hoffmann

Part 1

Concise Synthesis of Highly Substituted Isoquinolin-1-(*2H*)ones *via* IMDA

Chapter 1.
Introduction

1.1. General Introduction

Chemical synthesis deals with the transformation of matter to create new or already known molecules. This occurs *via* the breaking and forming of chemical bonds in predictable ways. The patterns that are applied for manipulating such changes are named chemical reactions. Therefore, chemical synthesis is comprised of two aspects; it can be used as a method to obtain a particular outcome (a desired molecule) or it can be perceived as an art that deserves improvement. To improve chemical synthesis, a deeper understanding of a reaction is necessary, so that its potency can be utilised in more productive ways (fewer side products leading to higher yields, reduced reaction time, a more comprehensive substrate scope, etc.). Chemical reactions which are more controlled will enable improved accessibility of desired molecules. These molecules have the potential for numerous applications such as plastics, dyes, drugs, etc.

A highly significant subgroup of chemical synthesis is organic synthesis. This field concentrates on the transformation of carbon-based chemical bonds. As a result of its close relationship with living systems (life being predominately based on carbon), organic synthesis has had a vast impact on medicine over the past century.

This thesis refers to the aspect of organic synthesis which aims to improve the art of methodology. In particular, the work aims to improve the field by achieving a better understanding of chemical processes and developing new methods based on the acquired knowledge.

This thesis is divided into two main projects; the first project is focused on the development of a new synthetic method based on the concise synthesis of highly functionalised isoquinoline-1(*2H*)-one derivatives. Concurrently, a second project was carried out with the aim of investigating and developing a thermal novel cascade reaction discovered within the Parsons' research group.

1.2. Introduction to Alkaloids

Alkaloids form a collection of complex nitrogen-containing compounds, derived from a range of sources such as microbes, marine organisms and plants through complex biosynthetic pathways. Alkaloids are a structurally varied class of nitrogen containing compounds and over 12,000 of these structures are derived from plants.[1] Alkaloids are located in 20% to 30%

of all flowering plants and are particularly common in some plant families such as *Fabaceae*, *Liliaceae*, *Solanaceae* and *Ranunculaceae*.[1] In addition, all species of *Papaveraceae* produce alkaloids. Alkaloids can emerge in all parts of the plant, although this depends on the plant species. More frequently, alkaloids accumulate in specific organs of the plant e.g. in bark, roots, leaves and fruits. Well known alkaloid compounds include purine alkaloids (caffeine **1.4**), tropane alkaloids (scopolamine **1.3** and cocaine **1.7**), benzylisoquinoline alkaloids (morphine **1.9** and berberine **1.13**) and monoterpenoid indole alkaloids (vinblastine **1.1** and ajmaline **1.2**).[2]

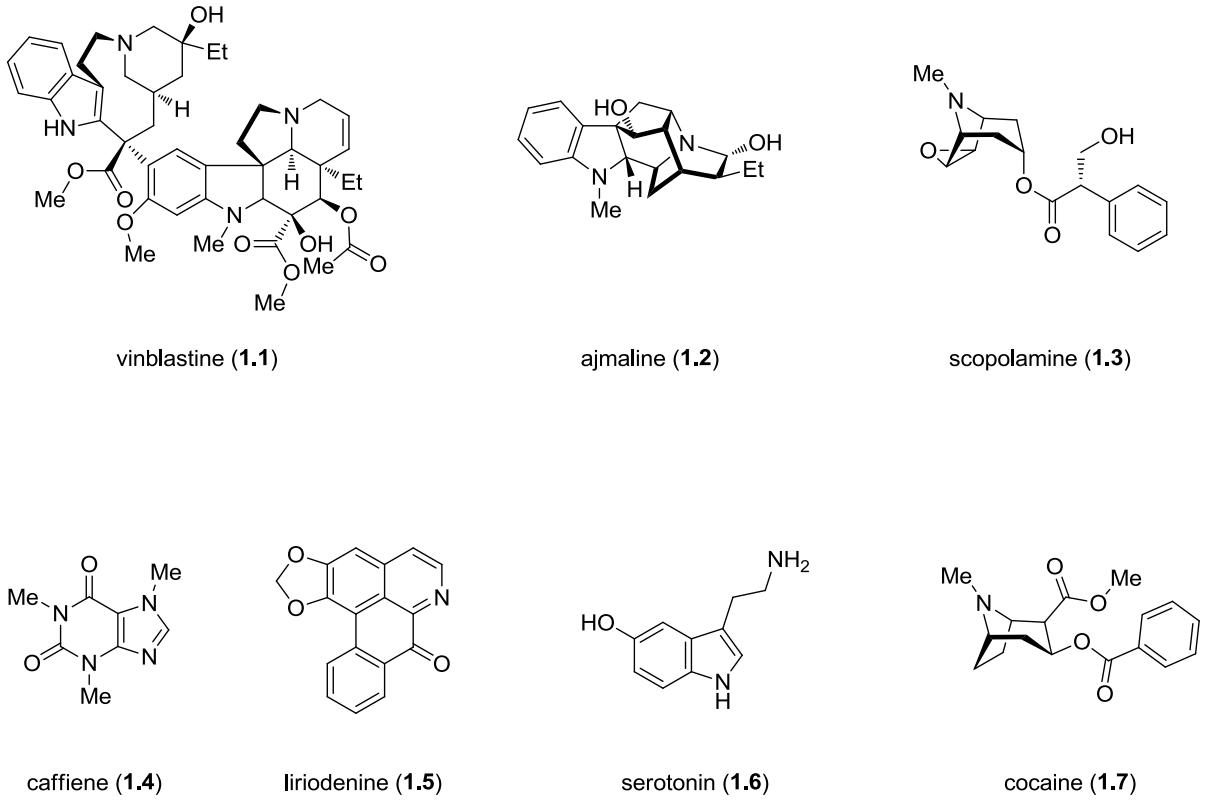


Figure 1.1: Examples of Well-Known Alkaloids

The function of alkaloids in plants is not always detectable and can vary, nevertheless it is believed that alkaloids contribute to a plants defence system against herbivores, improving the plants' overall growth, reproduction and survival.[3] For example, liriodenine **1.5** demonstrates antifungal activity defending the plant from parasitic fungi.[4] Alternatively, alkaloid substances such as serotonin **1.6**, perform an integral function in neurotransmission in both animals and humans.[5] The majority of alkaloids have a very bitter and disagreeable

taste, yet it is also put forward that alkaloids may function as a storage form of nitrogen and act as a protective agent against UV light damage.[3]

Alkaloids are moderately stable compounds, accumulating as the result of diverse biosynthetic pathways from amino acids e.g. lysine, ornithine, tyrosine and tryptophan. A small number are derivatives of terpenoids such as *Aconite* and are named pseudoalkaloids. In chemical terms they can be differentiated from other components by the presence of at least one nitrogen atom, but the majority also consist of oxygen. They are predominantly alkaline in nature which accounts for the name alkaloids, although some exceptions occur such as berberine **1.13** which is acidic. Furthermore, they are not normally water soluble and require organic solvents to be dissolved into, with ephedrine as an exception.

As the number of alkaloids reported has increased, so has the number of alkaloid families into which they are categorised. A nitrogen atom fixed in a specific carbon framework makes up the only defining structural feature of a given alkaloid.[6] The majority of alkaloids consist of complex polycyclic core structures that are largely responsible for their powerful and highly specific biological activity. Accordingly, any approach applied to these molecules will undoubtedly meet the challenge of nitrogen heterocycle synthesis. In spite of the structural diversity of alkaloids, the essential structural components located in these molecules are limited in variability. These motifs can be generally categorised into monocyclic *N*-heterocycles and benzannulated bicyclic systems. The majority of alkaloids such as the isoquinoline alkaloids are defined under the benzannulated bicyclic systems.

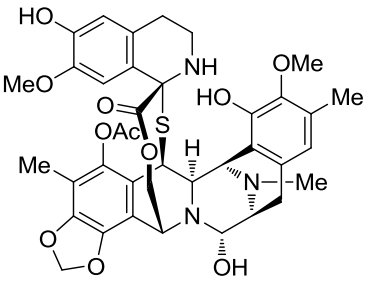
Although the extensive use of plants consisting of alkaloids with medicinal value began many centuries ago, the applications of alkaloids as isolated and characterized compounds initiated a new age of drug discovery starting in the 19th century.[7] A number of alkaloids of significant therapeutic value have been identified.[1] If the difficulty of obtaining alkaloids from natural origins in large quantities is considered, the significance of chemical synthesis as a potent means for solving supply issues in clinical trials and marketing is apparent. Consequently, the synthesis of alkaloids and their analogues has emerged as one of the most active research areas in modern organic chemistry.

1.2.1. Isoquinoline Alkaloids

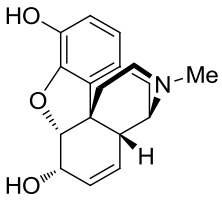
Isoquinoline, also referred to as benzo[*c*]pyridine or 2-benzanine, comprises of a benzene ring fused to a pyridine ring. Initially, it was isolated by Hoogewerf and van Dorp in 1885 as

a component of coal tar.[8] Additionally, it was disovered in the plants *Cistanche salsa* (Orobanchaceae), *Nicotiana tabacum cv* (Solanaceae), *Papaver somniferum* (Papaveraceae), and *Spigelia anthelmia* (Loganiaceae).[9] Isoquinoline is a significant structural mainstay in alkaloid natural products with the total number of isoquinoline alkaloids reported today reaching over 1,200. Alkaloids containing the isoquinoline ring as such or as part of a more complex ring system are not only numerous but also widely distributed. In addition, numerous classes of isoquinolines may occur simultaneously in plant families rich in alkaloids.

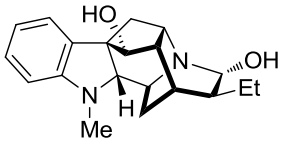
As a result of their biological activities, they are commonly utilised as building blocks in pharmaceutical compounds.[10] Also, they are used as chiral ligands for transition-metal catalysts[11] and their iridium complexes are applied in organic light-emitting diodes (LED).[12] For the purposes of refined natural product synthesis and the perfecting of biological and/or physical properties of those compounds for final use, a broad and malleable approach to this category of heterocycles is much desired. In addition, the approach must tolerate an extensive variety of functional groups.



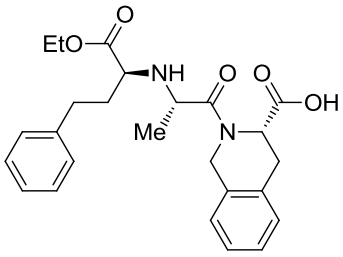
ecteinascidin 743 (**1.8**)



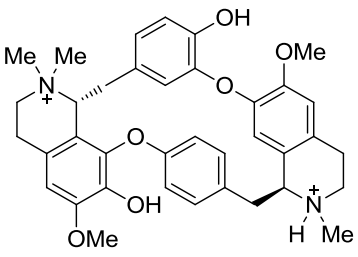
morphine (**1.9**)



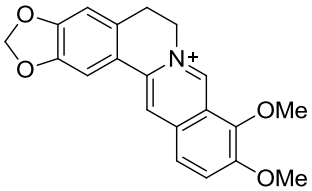
ajmaline (**1.10**)



quinapril (**1.11**)



tubocurarine (**1.12**)

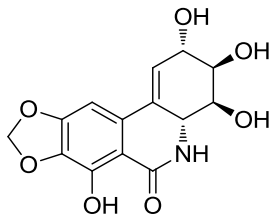


berberine (**1.13**)

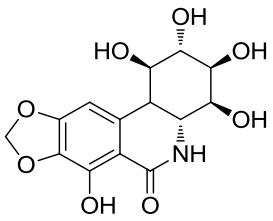
Figure 1.2: Biologically Active Natural Products Containing Isoquinoline Scaffold

1.2.1.1. Isoquinolin-1(*2H*)-ones

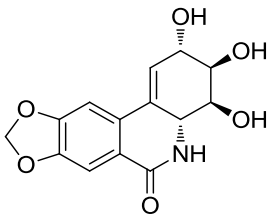
Isoquinolin-1(*2H*)-one is a regularly encountered structural sub-unit of many biologically active natural products e.g. narciclasine **1.14**, pancratistatin **1.15**, lycoricidine **1.16**, dorianine **1.17**, ruprechstyril **1.18** and thalifoline **1.19** as illustrated in **Figure 1.3**.[13]



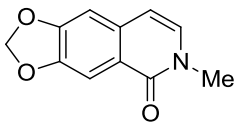
narciclasine (**1.14**)



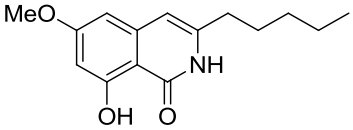
pancratistatin (**1.15**)



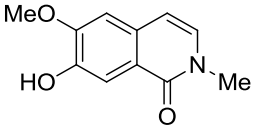
lycoricidine(**1.16**)



dorianine (**1.17**)



ruprechstyril (**1.18**)

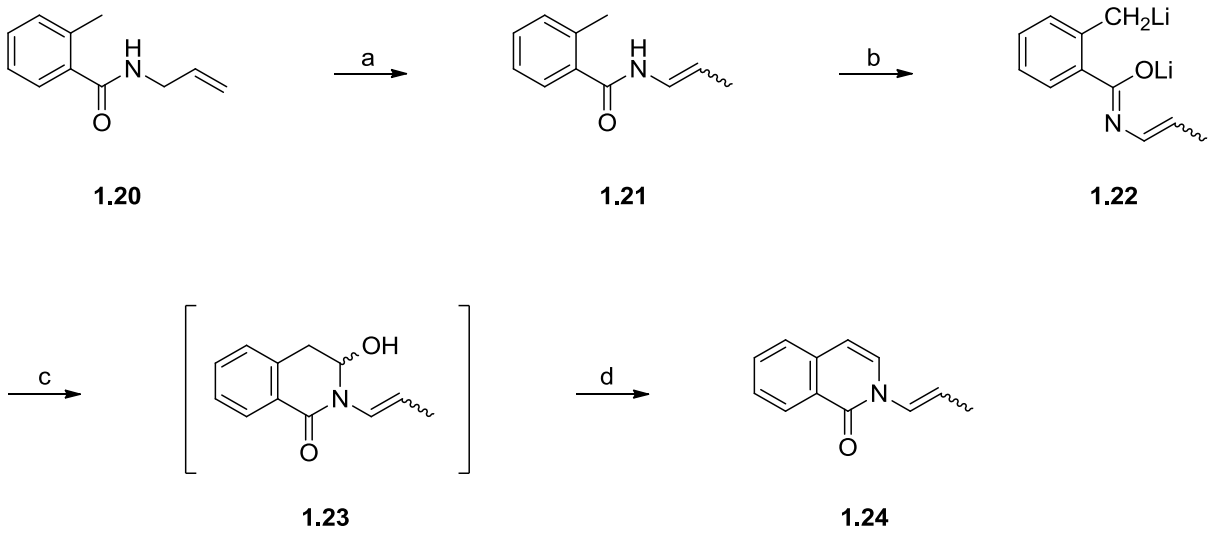


thalifoline (**1.19**)

Figure 1.3: Biologically Active Natural Products Containing Isoquinolin-1(*2H*)-one Scaffold

Isoquinolin-1(*2H*)-one derivatives have gained considerable attention on account of their antihypertensive and anticancer activities.[14] The wide range of biological activities demonstrated by the isoquinolin-1(*2H*)-one derivatives constitute an appealing and perplexing synthetic goal. Consequently, synthesis of substituted isoquinolin-1(*2H*)-one derivatives has accumulated notable attention.

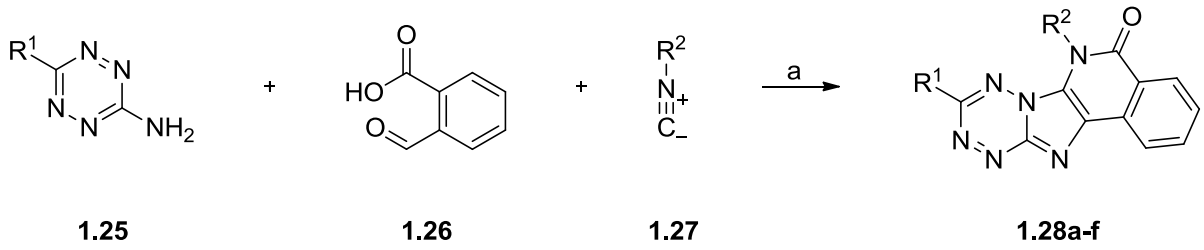
In 1992, Fisher *et al.*[15] demonstrated that the reaction of dilithio species derived from *N*-allyl-2-methylbenzamide with DMF, or other *N*,*N*-dimethyl amides, succeeded by acidic workup, yielded 2-propenylisoquinolin-l(*2H*)-one **1.24** or the 3-substituted derivatives.



Reagents and Conditions: (a) LDA (2.2 eq.), -70 °C to 0 °C, THF; (b) *sec*-BuLi (2.2 eq.), -70 °C, THF; (c) DMF (excess); (d) 1 M HCI (excess).

Scheme 1.1: Synthesis of 2-Propenylisoquinolin-l(*2H*)-one **1.24**

The well-known Ugi four-component condensation between aldehydes, isocyanides, amines and carboxylic acids typically affords *N*-substituted *α*-acylamino carboxamides.[16] Recently, Routier *et al.*[17] adopted this approach and synthesised new tetrazinoimidazoisoquinolinones **1.28a-f** by a microwave-assisted three-component reaction using aminotetrazine **1.25**, an isocyanide **1.27** and an *ortho*-carboxybenzaldehyde **1.26**.



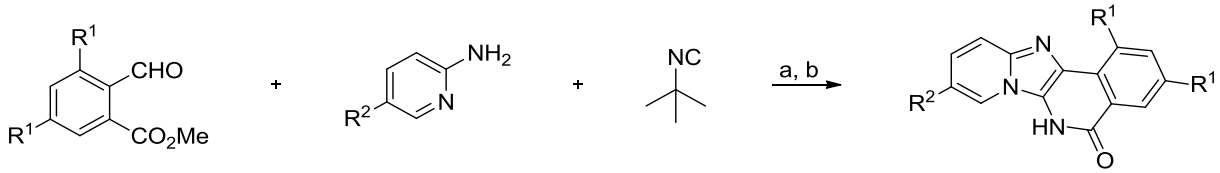
Reagents and Conditions: (a) Toluene, MW, 100 °C, 10 min., yields, see **Table 1.1**.

Scheme 1.2: Synthesis of Tetrazinoimidazoisoquinolinones **1.28a-f** by a Microwave-Assisted Three-Component Reaction

Compound	R^1	R^2	Yields(%)
1.28a	3,5-dimethyl-*1H*-pyrazol-1-yl	*c*-Hexyl	76
1.28b	3,5-dimethyl-*1H*-pyrazol-1-yl	*p*-methoxyphenyl	62
1.28c	3,5-dimethyl-*1H*-pyrazol-1-yl	2-Pentyl	trace
1.28d	Cl	*c*-Hexyl	61
1.28e	Cl	*p*-methoxyphenyl	trace
1.28f	Cl	2-Pentyl	53

Table 1.1: Synthesis of Tetrazinoimidazoisoquinolinones **1.28a-f**

Guchhait *et al.*[18] reported *in-situ* cyclisation of primary amine functionality mediated by de-*tert*-butylation in MCR products with tethered internal functional group. To this aim, Guchhait and co-workers selected phthalaldehydic esters **1.29** as the aldehyde component. The resultant Ugi-type multicomponent reaction with heterocyclic-2-amidines **1.30** and *tert*-butyl isocyanide **1.31**, together with the tandem dealkylation, generated the *in-situ* cyclised products isoquinolinoneimidazole-heterocycles **1.32a-c**.



1.29 **1.30** **1.31** **1.32a-c**

Reagents and Conditions: (a) $ZrCl_4$, *n*-BuOH, MW, 140 °C, 7 min.; (b) HBF_4, MW, 160 °C, 20 min., yields, see **Table 1.2**.

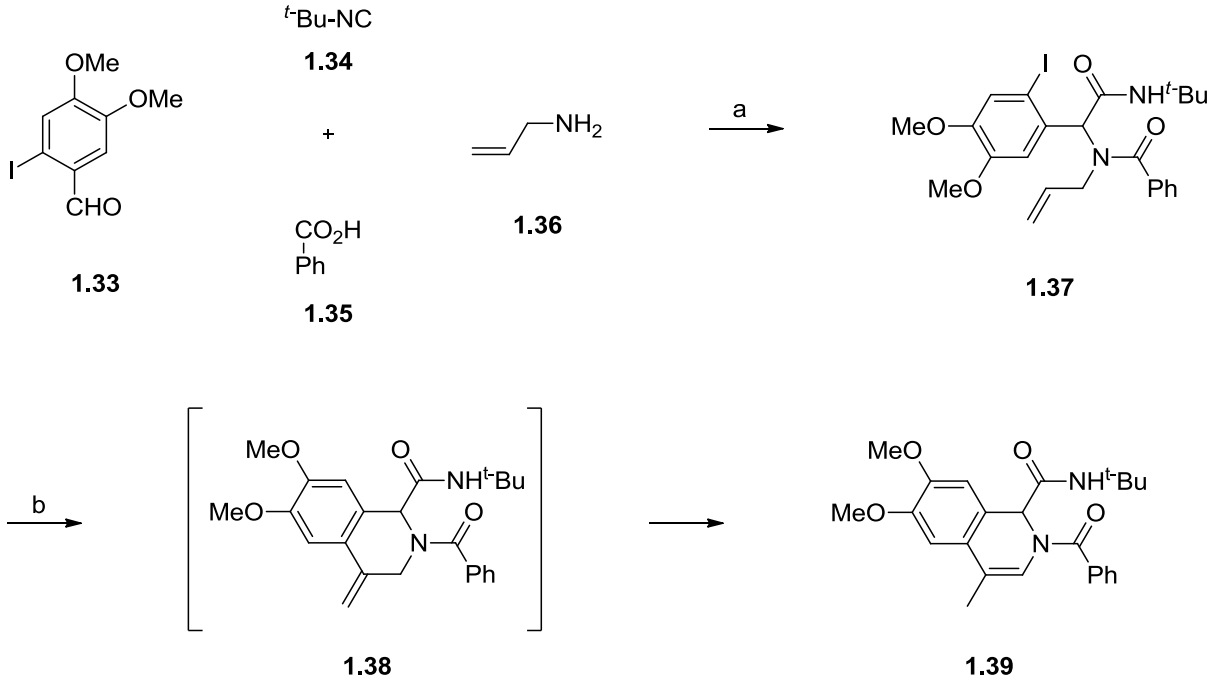
Scheme 1.3: One-Pot MCR-de-*tert*-Butylation Cyclisation: Synthesis of *N*-fused Isoquinolinone-Imidazole Heterocycles

Compound	R^1	R^2	Yields
1.32a	H	H	85%
1.32b	H	Br	72%
1.32c	OMe	H	80%

Table 1.2: Synthesis of *N*-fused Isoquinolinone-Imidazole Heterocycles

This original microwave-assisted tandem procedure of de-*tert*-butylation of the intermediate *tert*-butyl amine in an Ugi-type MCR product, yielded the effective implementation of *tert*-butyl isocyanide as a valuable convertible isonitrile. The authors concluded that this method may supply access to a varied array of medicinally-related *N*-fused heterocycles.

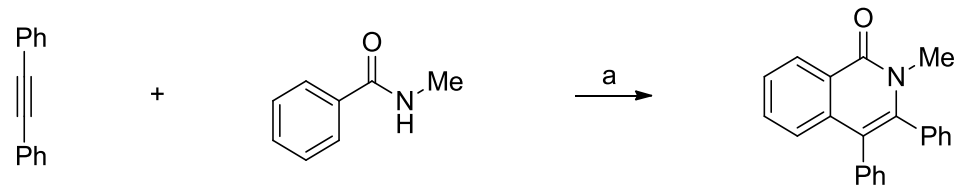
In 2004, Yang and co-workers also reported the synthesis of isoquinolin-1(*2H*)-one derivatives as a result of isocyanide based Ugi-MCR followed by a Heck reaction.[19] It was put forward that substrates comprising functionalities such as the Ugi product **1.37** can sequentially undergo the Pd-catalysed intramolecular Heck and double-bond isomerization to produce isoquinoline scaffolds **1.39** in one pot *via* the intermediates **1.38**.



Reagents and Conditions: (a) MeOH, 25 °C, 91%; (b) $Pd(OAc)_2$, PCy_3, DMA, 60 °C, *N*-methyldicyclohexylamine, 94%.

Scheme 1.4: Two-Step Synthesis of Isoquinoline **1.39**

During their studies on oxidative ruthenium-catalyzed homodehydrogenative arylations Ackermann and co-workers[20] observed ruthenium-catalyzed direct annulations of alkynes. Following these findings, they investigated the effect of contrasting reaction parameters on the oxidative annulation of alkyne **1.40** by amide **1.41**. Optimal yields of product **1.42** were obtained with $[\{RuCl_2(p\text{-cymene})\}_2]$, alongside $Cu(OAc)_2 \cdot H_2O$ as the terminal oxidant and *t*-AmOH (*t*-Am = *tert*-amyl) as the solvent.

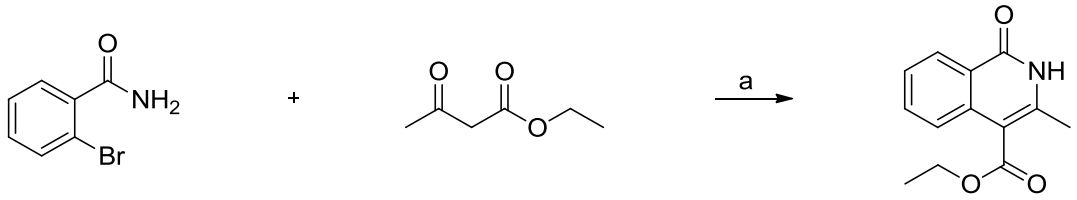


1.40 **1.41** **1.42**

Reagents and Conditions: (a) [{$RuCl_2$(*p*-cymene)}$_2$], $Cu(OAc)_2 \cdot H_2O$, *t*-AmOH, 100 °C, 22h, 76%.

Scheme 1.5: Ruthenium-Catalysed Synthesis of Isoquinolone **1.42**

Furthermore, Fu and co-workers established a copper catalysed procedure for the synthesis of isoquinolin-1(*2H*)-one derivatives *via* cascade reactions of *o*-halobenzamides with *β*-ketoesters.[21] A selected example is show in **Scheme 1.6** below.



1.44 **1.45** **1.46**

Reagents and Conditions: (a) CuI, Cs_2CO_3, dioxane, 80 °C, 16 h, 80%.

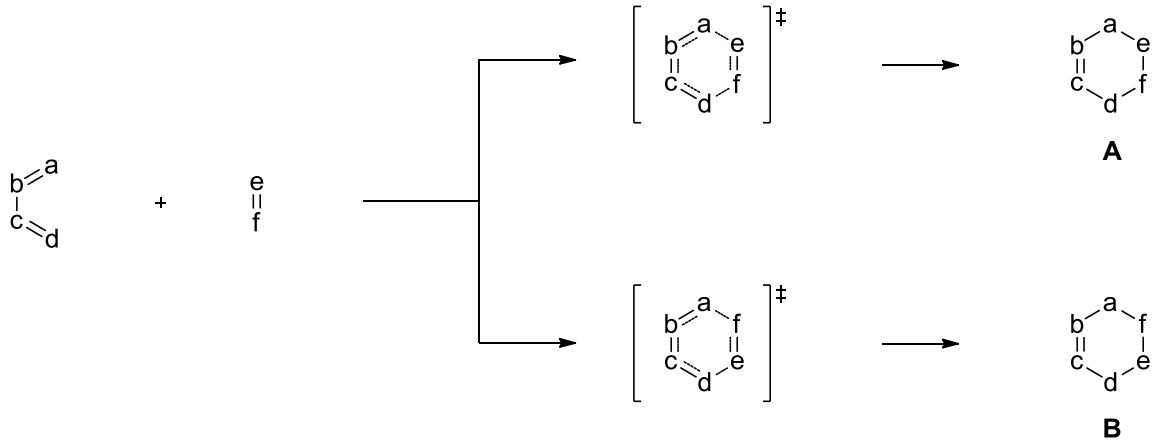
Scheme 1.6: Copper-Catalyzed Coupling of 2-Bromobenzamide with Ethyl Acetoacetate

Nevertheless, there are numerous methods available for the preparation of isoquinolin-1(*2H*)-one derivatives, yet a large majority endure a poor precursor scope with less points of diversity. A succinct synthetic methodology consisting of commercially accessible and affordable starting materials is still necessary for their practical synthesis.

1.3. The Diels-Alder Reaction

The product of a Diels-Alder (D-A) reaction (referred to as the "diene synthesis" in earlier accounts) is comprised of a six-membered ring, formed *via* fusion of a four-π component,

normally a *diene* and a two-π component, which is typically named the *dienophile* (**Scheme 1.7**).

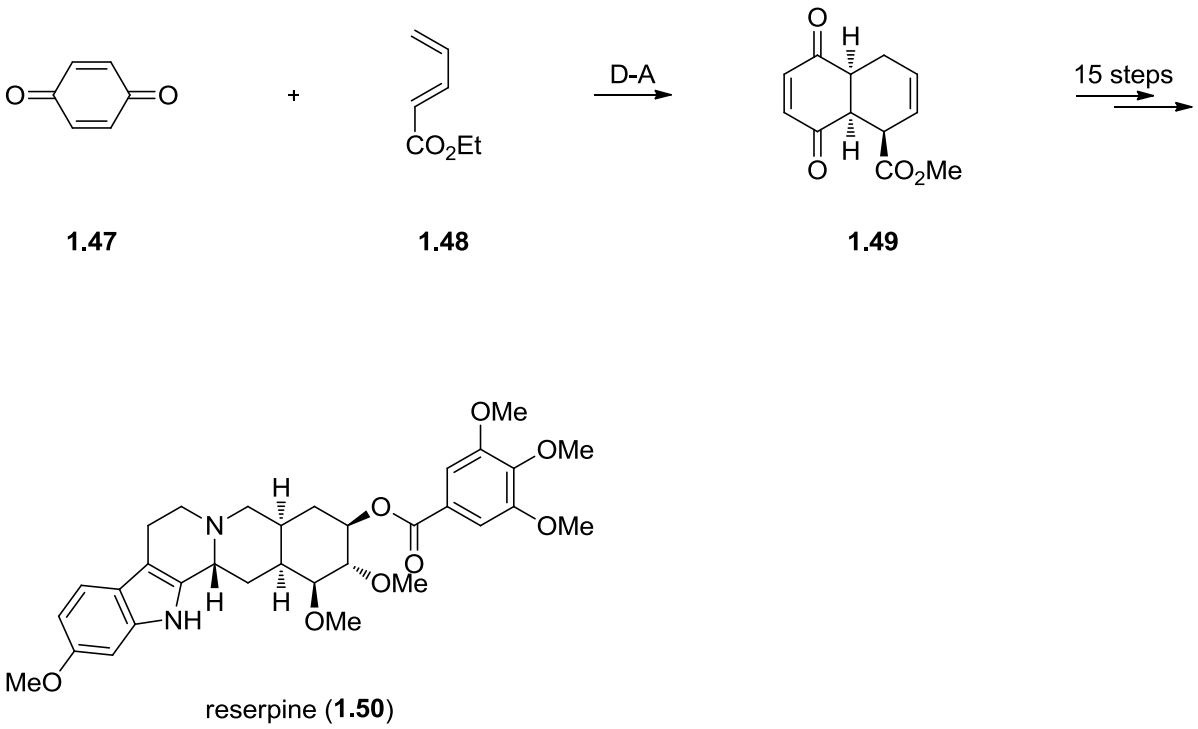


Scheme 1.7: Schematic Representation of the Diels-Alder Reaction (Structures **A** and **B** Indicate Two Regioisomeric Products)

The synthetic properties of the Diels-Alder reaction have proven to be of great significance, developing an important step in the formation of compounds comprised of six-membered rings.[22] Furthermore, configuration of the reacting double bonds are totally retained in the configuration of the product thus the reaction is stereospecific. Respectively, six novel stereocentres can be generated in a single reaction step and the absolute configuration of the two newly generated asymmetric centres can be effectively controlled.

The originally observed intermolecular Diels-Alder reaction has been expanded to consist of intramolecular reactions, hetero-Diels-Alder reactions, transannular reactions (TADA) and also diene-regenerative Diels-Alder reactions. The Diels-Alder reaction has been widely applied to the synthesis of natural products in account of its ability to produce increased molecular complexity.[22] Consequently, it is frequently used as the integral step during a synthetic strategy.

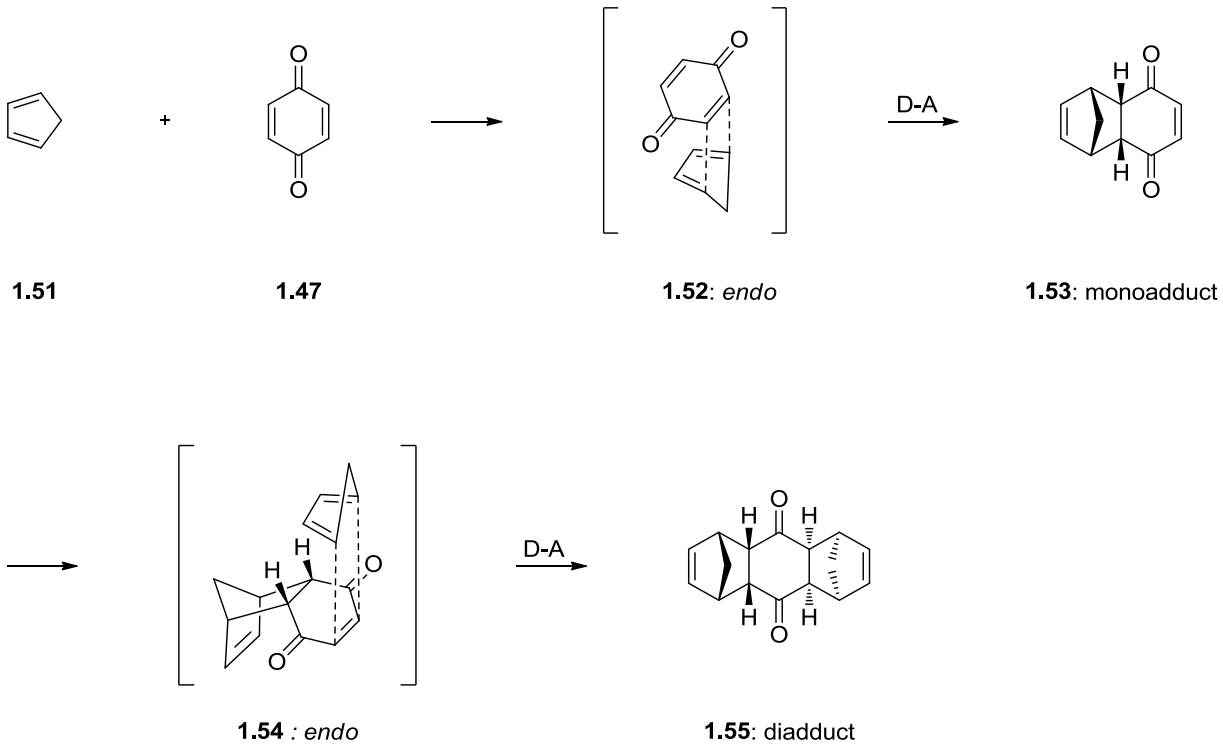
An early example of the Diels-Alder reaction in natural product synthesis was demonstrated by Woodward *et al.*[23] in 1956 in the total synthesis of reserpine. In this striking application, the Diels-Alder was used to establish the first three of the six stereocenters of the molecule in one novel step. Following this first step, the rest of the molecule was expounded in fifteen more chemical steps, illustrating the utility of the Diels-Alder reaction in attaining products of high complexity.



Scheme 1.8: The Total Synthesis of Reserpine by Woodward *et al.*[23]

1.3.1. The History

The synthetic and theoretical aspects of this reaction were studied in great detail by the German chemists Otto Diels and Kurt Alder, whose names were subsequently given to the reaction. On the contrary to popular belief, the reaction was not the discovery of Diels and Alder, yet they were awarded the Nobel Prize in 1950 for their extensive work towards its investigation. The original example of a Diels-Alder reaction (specifically the dimerisation of tetrachlorocyclopentadienone) dates from 1892.[24] Von Euler was the first chemist to recognise the significance of the reaction in 1920,[25] although the structures of the products were inaccurate. In 1928, Otto Diels and Kurt Alder were responsible for identifying the accurate structure of the products (**1.53** and **1.55**), resulting from the reaction of cyclopentadiene **1.51** with quinone **1.47**.[26]



1.51 **1.47** **1.52**: *endo* **1.53**: monoadduct

1.54 *: endo* **1.55**: diadduct

Scheme 1.9: The Discovery of the Diels-Alder (D-A) Reaction in 1928[26]

Diels and Alder were clearly aware of the significance of this discovery, particularly as applied to natural product synthesis and predicted the realisation of new-found possibilities; *"Thus it appears to us that the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps even alkaloids, has been moved to the near prospect".*[26]

1.3.2. Mechanistic Aspects

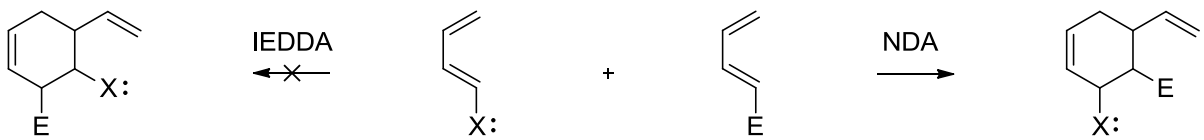
The Diels-Alder reactants can comprise of only hydrocarbon fragments (*homo-Diels-Alder reaction*), but it is also possible that they contain one or more heteroatoms on any of the positions a-f (*hetero-Diels-Alder reaction*) culminating in heterocyclic ring systems (**Scheme 1.7**). The combinations of carbon and hetero atoms which was readmitted are highly varied, reflecting the significant versatility of this reaction.[22]

In Diels-Alder reactions, a notable division is made between *normal electron demand* and *inverse electron demand* additions. The basis for this distinction is the rate of the reaction response to the introduction of electron withdrawing and electron donating substituents.

Normal electron demand Diels-Alder reactions (NDA) are advocated by electron donating substituents on the diene and electron withdrawing substituents on the dienophile. On the contrary, inverse electron demand Diels-Alder reactions (IEDDA) are expedited by electron withdrawing substituents on the diene and electron donating ones on the dienophile. In addition, there is an intermediate class; the neutral Diels-Alder reaction that is expedited by both electron withdrawing and donating substituents.

The *Frontier Molecular Orbital (FMO) theory* can rationalise the way in which the substituents affect the rate of the reaction.[27] The FMO theory emerged during a study of the role of orbital symmetry in pericyclic reactions by Woodward and Hoffmann[28] and independently, by Fukui.[29] Subsequently, Houk[30] advanced knowledge on the reactivity and selectivity of these processes.

Two modes of interaction are possible when FMO is applied to the Diels-Alder reactions, the reaction is controlled by either the HOMO of the diene and the LUMO of the dienophile (*normal electron demand*) or the interaction between the LUMO of the diene and the HOMO of the dienophile (*inverse electron demand*). In the first mode, a decrease in the HOMO diene–LUMO dienophile energy gap can be enhanced by either increasing the energy of the HOMO of the diene *via* the addition of electron donating substituents, or decreasing the energy of the LUMO of the dienophile by the addition of electron withdrawing substituents. The HOMO diene–LUMO dienophile interaction exerts a greater influence on the energetics of the Diels-Alder reaction when compared with the HOMO dienophile–LUMO diene interaction.[31] Perhaps the most persuasive experimental evidence for this hypothesis comes from the observation by Spiro *et al.*[32] that normal electron demand Diels-Alder cycloadditions are consistently preferred over inverse electron demand Diels-Alder cycloadditions in the cross-Diels-Alder cycloaddition between an electron-poor and an electron-rich diene.[32]



1.57 **1.56** **1.58** **1.59**

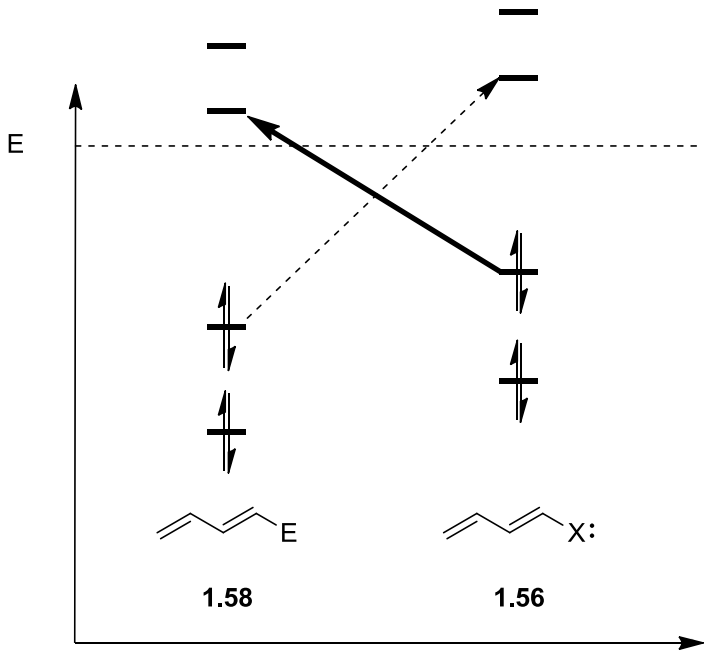


Figure 1.4: The NDA is always favoured over the IEDDA in Cross-Diels-Alder Cycloadditions

Although many reactions do not adhere to the FMO rule of reactivity,[33] inverse electron demand Diels-Alder cycloadditions have an excessive amount of examples in that category. For instance, the dimerization of acrolein competes successfully with its cycloadditions with electron-rich dienophiles in spite of typical energy gaps that gives the latter 1.5-2.0 eV advantage.[34] Also, 2-carbomethoxy-1,3-butadiene dimerises much faster than it reacts with dihydropyran and other electron-rich dienophiles.[35] In the example of normal electron demand Diels-Alder cycloadditions, the FMO theory may estimate the relative reactivities between dienophiles, although in the example of inverse-electron demand Diels-Alder reactions, it may not. Interestingly, Spiro *et al.*[32] demonstrated that the dissymmetry in electron-rich dienophiles escalates their reactivities.

According to Woodward and Hoffmann (W-H), the formation of two new δ-bonds preserves orbital symmetry thus enabling the reaction to be *concerted*; this is illustrated in **Figure 1.5**. This is in line with the general idea that needless geometric distortions in the course of reactions should be avoided as much as possible to take the minimum-energy trajectories. In other words, no intermediate is included in pericyclic processes like the Diels-Alder reaction.[36] Furthermore, a significant number of computer simulations were consistant with a concerted mechanism.[37]

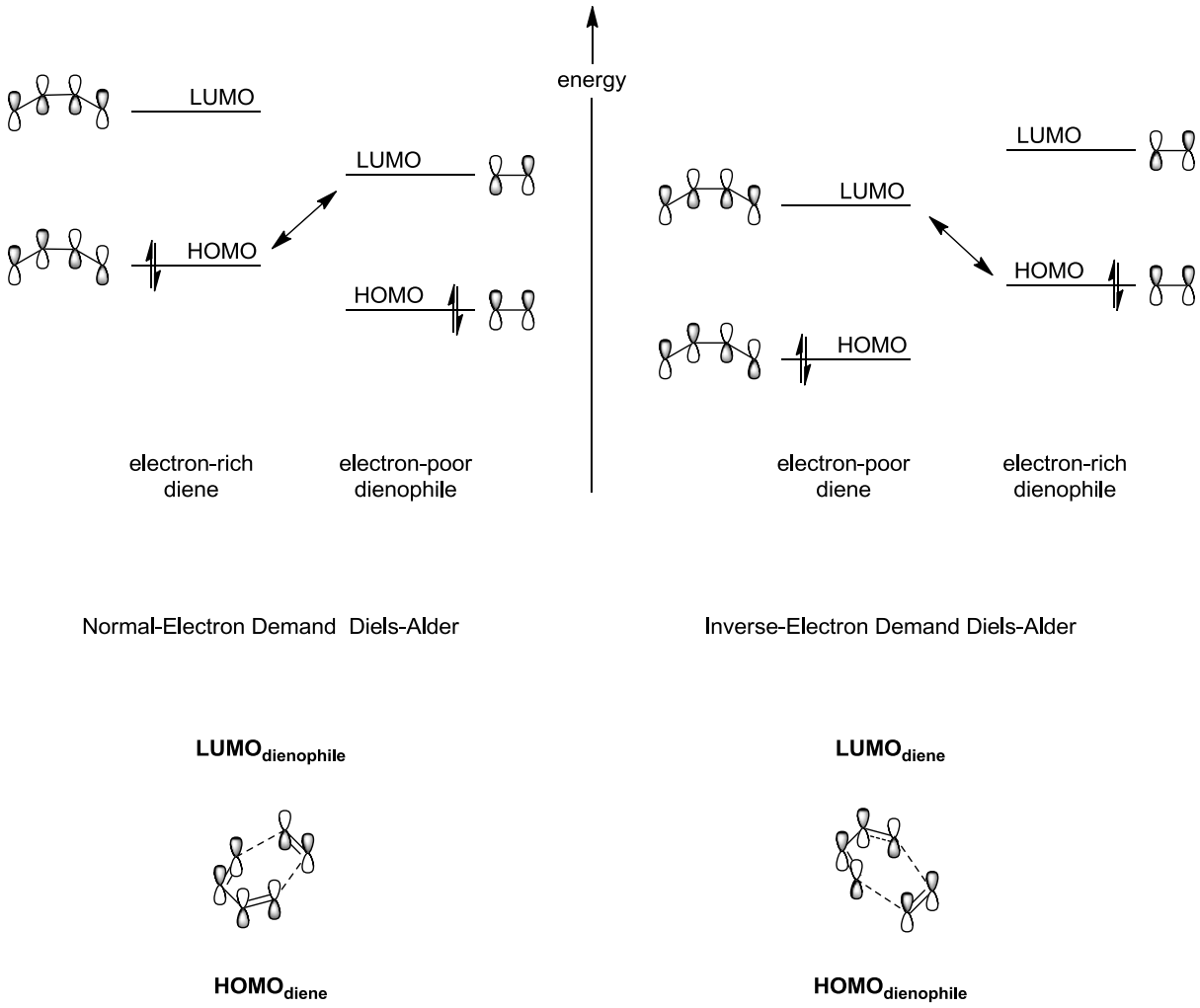
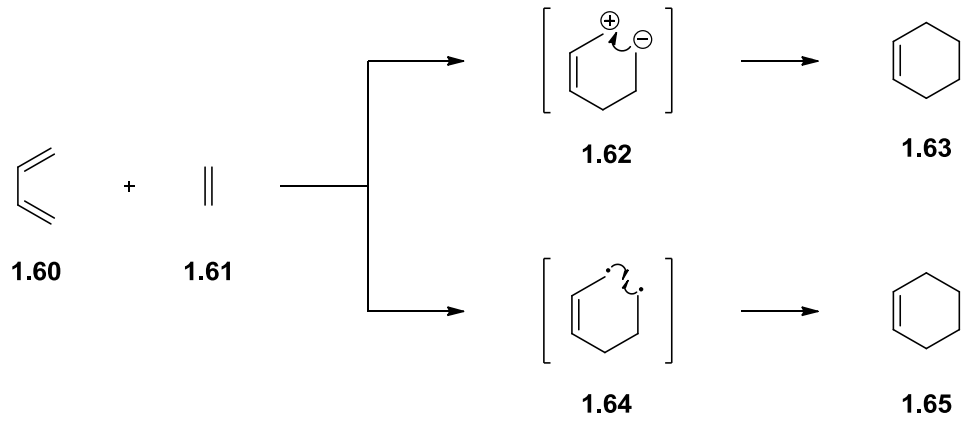


Figure 1.5: Distinction between Normal- and Inverse-Electron Demand Diels-Alder Reactions

Regardless of this vast body of evidence, two-step mechanisms have been proposed for the Diels-Alder reaction. It is likely that special cases have accounted for this, where highly substituted dienes and/or dienophiles have been observed to react *via* zwitterionic[38] or' biradical[39] intermediates (**Scheme 1.10**).



Scheme 1.10: Schematical Representation of a *zwitterionic* and a *biradical* Pathway of a Diels-Alder Reaction

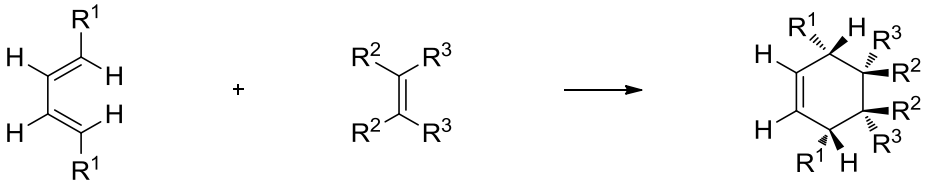
In comparative kinetic studies, the rate of ion formation from *p*-substituted α,α-dimethylbenzyl chloride was shown to increase by 10^9 when the *para* substituent reforms from a methoxy into a nitro group. Similarly, a change in substituent in the Diels-Alder reaction of *p*-substituted 1-phenylbutadienes with maleic anhydride renders an increase in the rate by only tenfold (10^1). This difference suggests that the cycloaddition is not ensuing *via* a zwitterionic mechanism. Furthermore, [4+2] reaction rates in the gas phase are analogous to those in solution, from which follows the conclusion that any intermediate could only be marginally more polar than the ground state as solvation is unnecessary. The prospect of a biradical singlet intermediate has been implied by some studies, although this may be dependent on the type of substrates used in the reaction.[40]

One of the more notable arguments in support of the multicentered mechanism is the universal, stereospecific *cis* addition of dienophile to diene known as the "*cis*" principle. In this example, the steric arrangements of substituents on both reactants are conserved within the adduct. If the substituents are *trans* on the dienophile for instance, they will stay *trans* in the product. This observation is typically understood to indicate a synchronous formation of bonds. However, Sauer *et al.*[41] suggested that this does not entirely rule out the possibility of a two-step reaction. If the ring closure step is very fast, the prospect for rotation about the C-C bond axis during an intermediate transition step would be non-existent and the *cis* principle would remain upheld. However, following extensive calculations an agreement was reached in preference of the concerted mechanism.[42,43,44] The concerted nature of the reaction does not indicate that in the activated complex the magnitude of formation of the two new *δ*-bonds is necessarily equivalent. Asymmetric substitution arrangements on the diene and/or

dienophile can result in an *asynchronous* activation process.[45] The magnitude of asynchronicity can be estimated from the FMO-coefficients of the terminal carbons of diene and dienophile. The FMO coefficients also permit qualitative estimation of the kinetically controlled *regioselectivity*.

Although the Woodward-Hoffmann rule and FMO theory both share a degree of success, there remain issues of clarity in both accounts. To address this uncertainty, Fukui put forward a theory of intrinsic reaction coordinate (IRC)[46] and aimed to connect analytically the perturbative region with TS. The current progress on IRC calculations[47] enables the possibility of tracing the symmetry-allowed paths in realistic reacting systems.

Diels–Alder reactions consisting of asymmetrically substituted reactants will proceed through an asymmetric transition state.[48] However, even symmetrically substituted reactants can induce an asymmetric transition state. In recent work, Yamabe *et al.*[49] examined paths of a variety of normal electron demand Diels-Alder reactions with density functional theory calculations. In this work, paths of Diels-Alder reactions of dienes and olefins with symmetric geometries were discerned.



1.66 **1.67** **1.68a-d**

1.68a $R^1 = R^2 = R^3 = H$ **1.68b** $R^1 = H,\ R^2 = R^3 = CN$

1.68c $R^1 = OMe,\ R^2 = H,\ R^3 = CN$ **1.68d** $R^1 = OMe,\ R^2 = R^3 = CN$

Scheme 1.11: Diels-Alder Reaction between Linear Dienes and Dienophiles

In accordance with the symmetry-allowed condition, TS geometries of parts **1.68a**, **1.68b** and **1.68c** have *Cs*-symmetry. However, that of part **1.68d** was found to be asymmetric. In part **1.68d**, one bond-forming C···C distance is 1.926 Å and the other is 2.564 Å. The combination between a highly nucleophilic diene; (*E*,*E*)-1,4-dimethoxy-1,3-butadiene (DMB) and a highly electrophilic olefin; tetracyanoethylene (TCNE), has broken the W-H rule. While many reactions take the *Cs*-symmetry paths obeying the W-H rule, those of strong nucleophilic dienes and electrophilic olefins do not follow the symmetry-conservation rule.

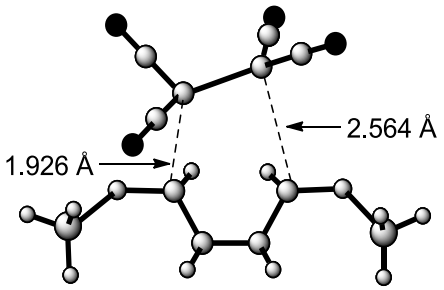


Figure 1.6: Transition-State (TS) Structure of Diels-Alder Reaction between Linear Diene and Dienophile

When symmetrically distributed substituents are placed on Diels–Alder adducts, the reaction's transition state can be of *Cs*-symmetry or it can be asymmetric.[49] The symmetry nature of the TS depends on an interplay between orbital interactions, aromaticity (which favors a *Cs* structure) and strain (which tends to break symmetry). Bachrach and co-workers examined several Diels-Alder reactions involving only alkyl substituents to minimize the role of orbital interactions.[48] The approximation of strain energy was reached by taking the difference in energy between either reactants or products in their most constant conformation and relating them to the energy of the symmetry-constrained conformation. This measure of strain energy was subsequently used to separate the reactions into two divergent groups. The reactions with a strain energy of less than 10 kcal mol^{-1} occur with a symmetric transition state and those reactions with a strain energy in excess of 10 kcal mol^{-1} proceed with an asymmetric transition state. As a first approximation, authors estimated that the aromatic stabilisation energy in the TS is about 10 kcal mol^{-1}.[48]

A particularly significant factor in the concerted Diels-Alder reaction is the conformation of the diene. In order for the dienophile to interact simultaneously with the orbitals on either end of the diene, the diene must adopt a "*s-cis*" conformation, though it need not be planar. A diene locked in the "*s-trans*" conformation will not undergo a Diels-Alder reaction. In a large number of acyclic dienes such as 1,3-butadiene, the "*s-trans*" conformation takes control and the Diels-Alder reaction is a slow procedure. Consequently, dienes locked in the "*s-cis*" conformation are considerably more reactive. Understanding that the "*s-cis*" conformation is normally higher in energy than the "*s-trans*" conformation makes the association with strain energy apparent. For example, some strain is intrinsic in a Diels–Alder reaction consisting of any acyclic diene. A symmetric transition state must overcome even more strain, given that constraining the diene to be planar and all substituents to totally eclipse will demand

additional energy. The driving-force for adopting this symmetrical arrangement is the stabilization related to aromaticity. The occurrence of the reaction *via* an asymmetric TS is not strain-free but rather it selects this path so as to minimise the strain. Cyclopentadiene is a key example of a locked "*s-cis*" diene and accordingly, is a highly reactive diene for the Diels-Alder reaction.

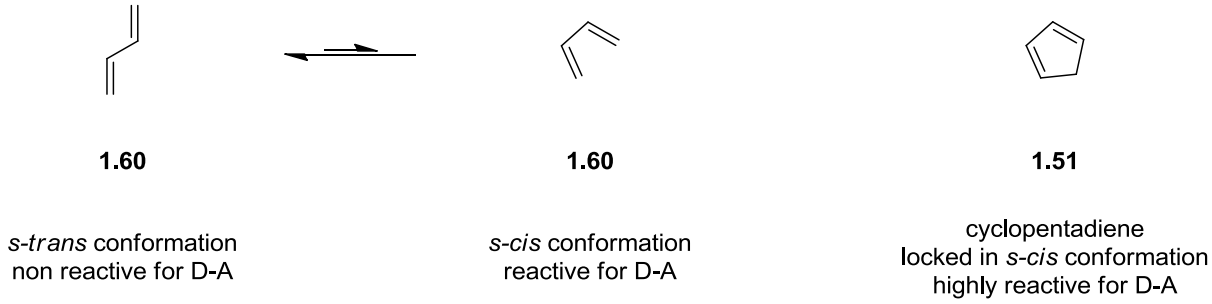
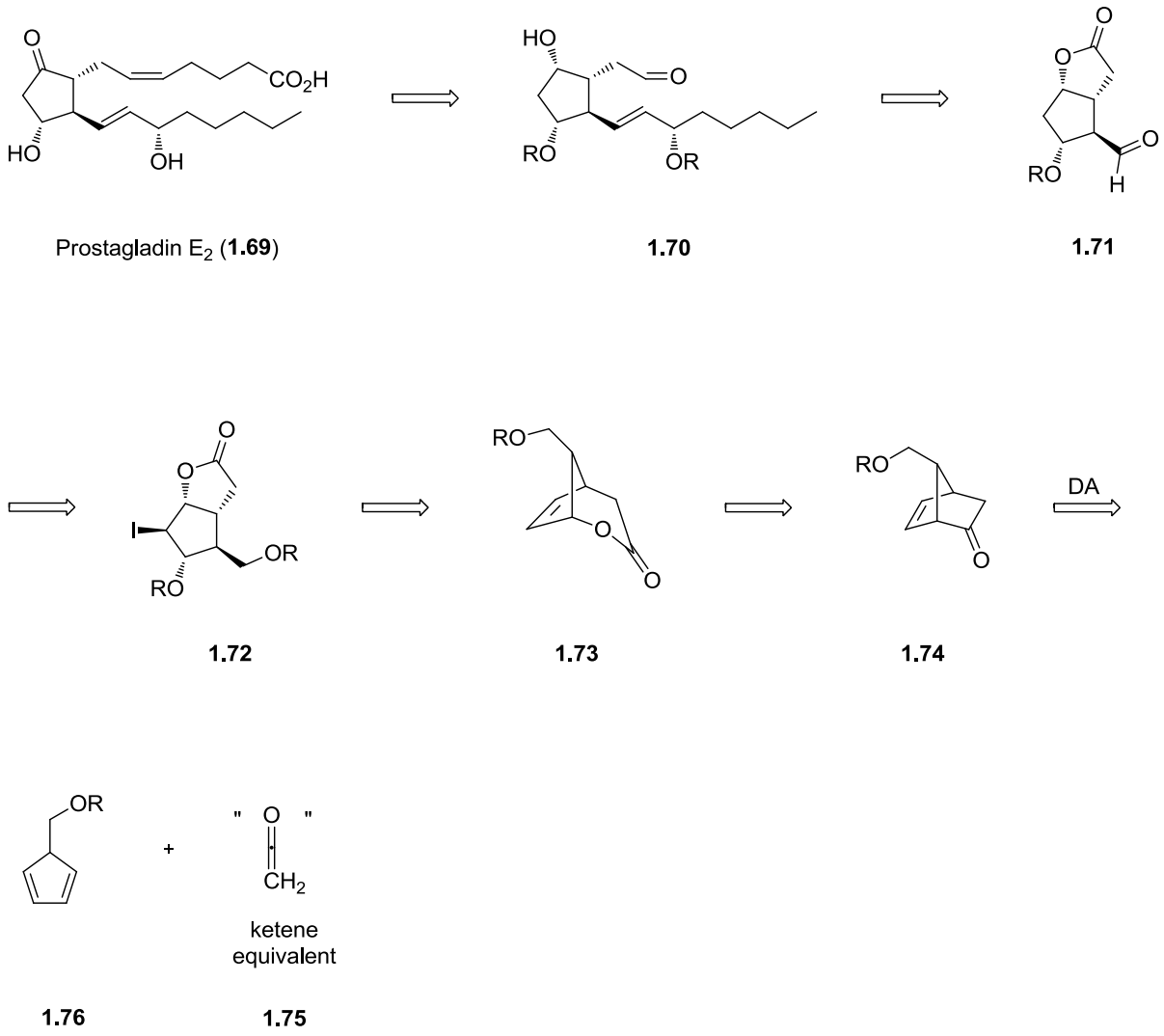


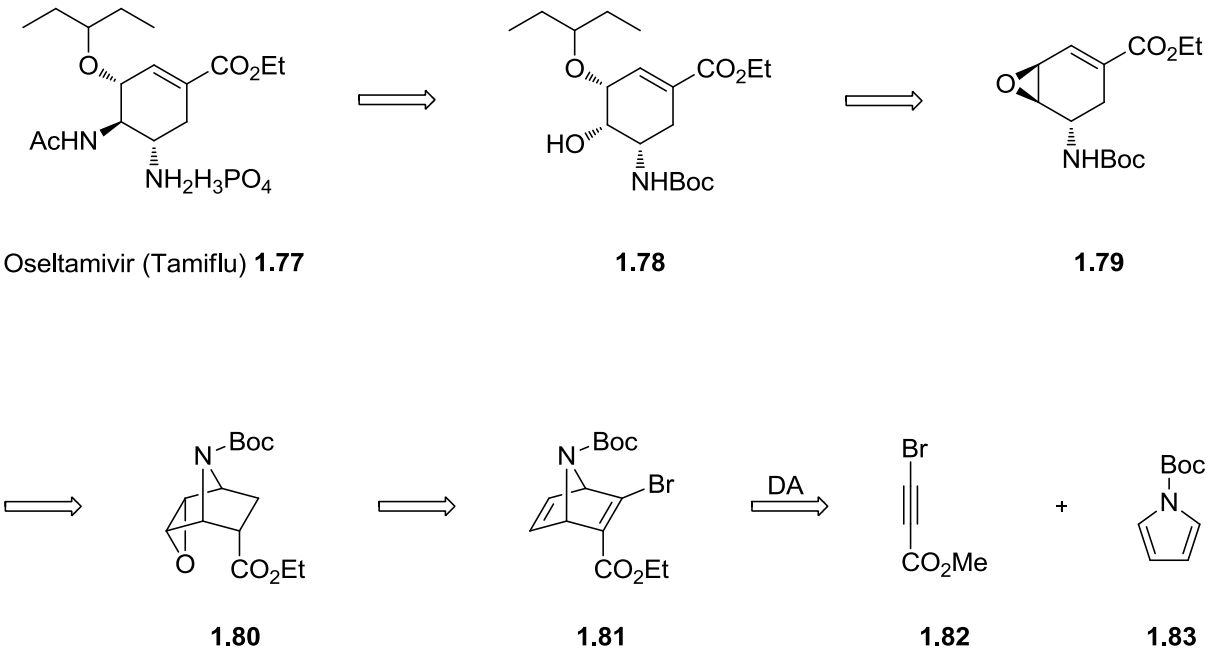
Figure 1.7: Diene Conformation Affecting the Reactivity in Diels-Alder Reactions

A classical, demonstrative example of the use of cyclopentadienes in the Diels-Alder context is E. J. Corey's ground-breaking work on the total synthesis of the prostaglandins.[50] The retrosynthesis of the desired prostaglandin core derives from the late disconnection of the top side-chain. Subsequently, the bottom side-chain is disconnected which leads to a cyclopentane core.



Scheme 1.12: Retrosynthetic Analysis of the Corey Approach to the Prostaglandins

Alternatively, the aromatic five-membered-ring heterocycles are also defined as 1,3-butadiene derivatives. The diene-like chemical behaviour may be demonstrated in such a manner. Primary examples of locked "*s-cis*" aromatic five-membered-ring heterocycles are furan and pyrrole. Pyrrole is an aromatic ring and is unreactive towards the Diels-Alder reaction. Nevertheless, pyrrole derivatives develop into good dienes in the Diels-Alder reaction with electron-poor dienophiles when an electron-withdrawing group is installed at the N1 position. Accordingly, formal syntheses of Tamiflu® from the Diels-Alder adduct of a pyrrole and acetylene was recently reported by Kamimura *et. al.*[51]

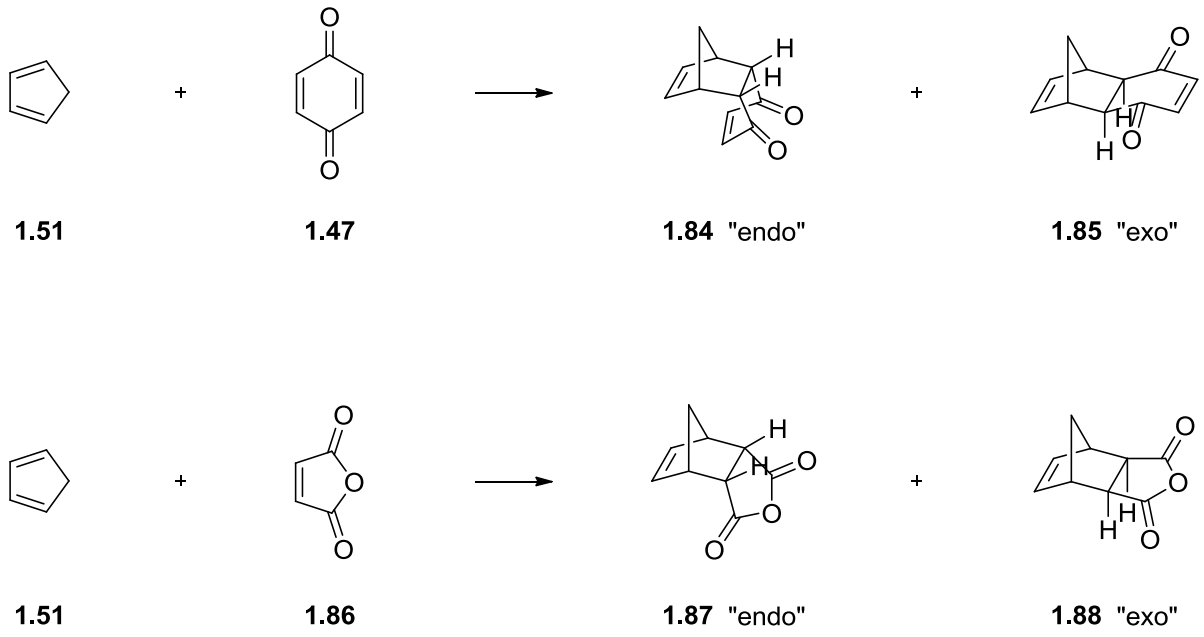


Oseltamivir (Tamiflu) **1.77** **1.78** **1.79**

1.80 **1.81** **1.82** **1.83**

Scheme 1.13: Retrosynthetic Analysis of the Kamimura Approach to Tamiflu®

An additional form of selectivity can emerge when substituted dienes and dienophiles are utilised in the Diels-Alder reaction. Two alternative cycloadducts denoted as *endo* and *exo* can subsequently be formed (**Scheme 1.14**). Alder and Stein discerned that there usually exists a propensity for formation of the *endo* isomer,[52] although this has been the subject of some criticism.[53] According to *Alder's rule*, the major stereoisomer in Diels-Alder reactions is the one that is formed by maximum accumulation of double bonds in the transition state (through-space).[54] On the other hand, the *endo* product is usually less stable than *exo*. While the stereoelectronic interactions involved in the transition state stability are widely studied in the literature,[55] the same attention has not been dedicated to understand the stability of the products. One of the most used examples of the Diels-Alder reaction[56] is the reaction between cyclopentadiene **1.51** and maleic anhydride **1.86**. At room temperature, this reaction gives only the *endo* adduct that is then converted at 200 ºC to the thermodynamically more stable *exo* adduct through a retro Diels-Alder reaction.[57] Similarly, according to several authors[58] the Diels-Alder reaction between cyclopentadiene **1.51** and 1,4-benzoquinone **1.47** produces only the kinetic *endo* adduct **1.84**, although the *exo* adduct **1.85** has higher stability than the *endo* adduct **1.84** due to the steric repulsive interaction present in the *endo* form.



Scheme 1.14: *Endo/Exo* Selectivity in [4+2] Cycloaddition of 1,4-Benzoquinone and Maleic anhydride with Cyclopentadiene

Nevertheless, the theoretical calculation for the cycloaddition reaction of 1,4-benzoquinone **1.47** and cyclopentadiene **1.51** indicates that the energy for *exo* transition state structure is 1.8 kcal mol^{-1} higher than for *endo* which supports the observed experimental results (**Figure 1.8**).[59] On the contrary, recent analysis on the energies of the products indicated that the *endo* adduct was more stable (thermodynamic product) than *exo* which discounts the literature data.[60] Also, the data supported that in the *endo* adduct the steric repulsive interactions are greater than in *exo*. However, the attractive delocalization interaction in *endo* is higher than in *exo* and counterbalances the steric repulsion. This explains why the *endo* **1.84** and not the *exo* **1.85** is additionally the thermodynamic product, as confirmed in the current literature.

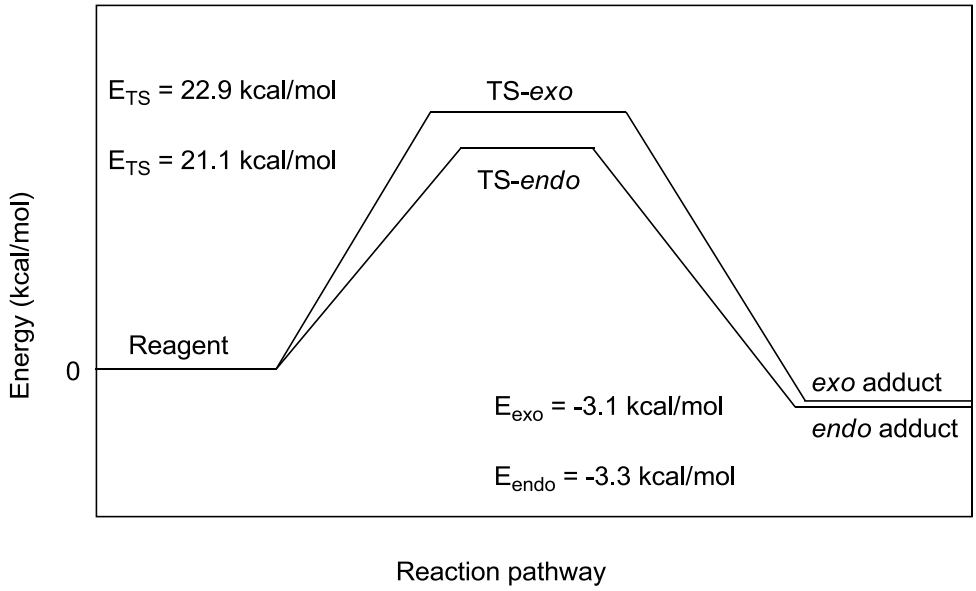


Figure 1.8: Energies for *endo* and *exo* Reaction Pathways of the Cycloaddition Reaction of Cyclopentadiene **1.51** and 1,4-Benzoquinone **1.47**

The interactions intrinsic to this behaviour have been the topic of extensive research. Considering that the reactions leading to *endo* and *exo* products have the same initial state in common, the discrepancies between the respective transition-state energies completely justify the reported selectivity. The theory that *Secondary Orbital Interactions* are of primary significance was proposed by Woodward and Katz.[61] Cossio *et al.*[62] presented a method to measure the *Secondary Orbital Interaction* (*SOI*). The application of this method to the cyclopentadiene **1.51** - maleic anhydride **1.86** cycloaddition, indicates notable stabilization of the *endo* transition state in account of *Secondary Orbital Interaction*. As a result of these findings the authors concluded that "*SOI do exist and are responsible for at least an important part of the observed stereocontrol*".

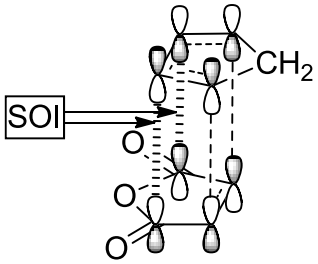


Figure 1.9: The *endo* Approach for the Cyclopentadiene **1.51** – Maleic anhydride **1.86** Reaction

In contrast, analysis of the parallel approximation between *s-trans* butadiene and fumaronitrile indicated that *SOI* was overrun by closed-shell repulsions.[63] Additionally, the research of several reactions (cyclobutadiene-norbornadiene, cyclopentadiene-maleic anhydride, cyclobutadiene-cyclobutenedione) reported the absence of a net attraction for the atom pairs associated in *SOI*. In conclusion of these results the authors stated "*the endo preference is not due to the occurrence of an attractive interaction between the atom pairs involved in SOI and so this concept is unnecessary*".

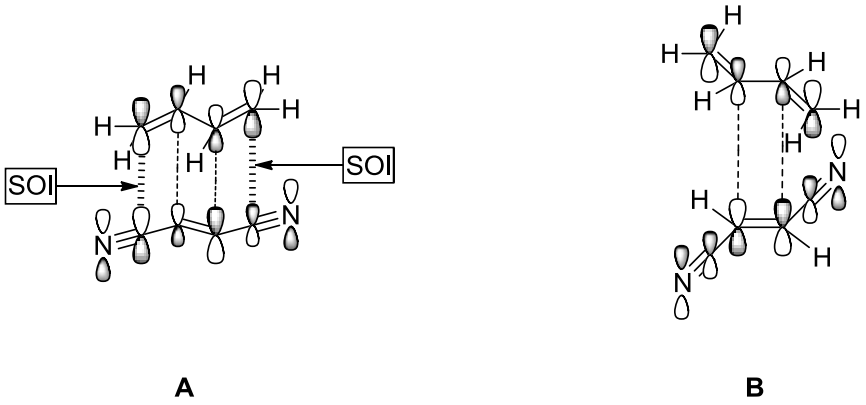


Figure 1.10: *s-trans*-Butadiene + fumaronitrile Complexes that have (**A**) or lack (**B**) *SOI*

This account has also been criticised by Mellor, who accredited the *endo* selectivity to steric interactions.[64] Steric effects are commonly suggested as significant in determining the selectivity of Diels-Alder reactions, especially of substituted dienophiles and may eventually lead to *exo*-selectivity.[65] In the case of other systems, steric effects in the *exo* activated complex can augment *endo* selectivity.[66,67] For instance, the *endo* preference observed in the cycloadditions of cyclopentadiene **1.51** with some alkenes (such as cyclopentene or *cis*-3,4-dichlorocyclobutene) is commonly attributed to steric repulsion between the methylene group of the diene and the substituents of the dienophile.[68]

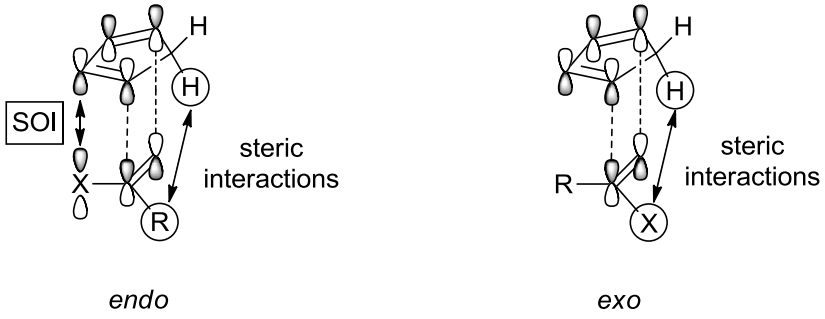


Figure 1.11: Alternative Interactions Proposed in Order to explain the *endo* Preference Found in the Diels-Alder Reactions of Cyclopentadiene **1.51** with Various Dienophiles

Nonetheless, it can be suggested that the *endo* preference of Diels-Alder reactions of cyclopentadiene with numerous α,*β*-unsaturated carbonyl compounds could also be justified in terms of *SOI* (**Figure 1.11**).[69] However, experimental data (shown in **Table 1.3**) illustrate that a methyl group induces a greater *endo* preference than carbonyl-bearing substituents (COOH, CHO, $COOCH_3$).[70] This outcome is in accordance with the greater size of the methyl group as construed from experimental data on the axial/equatorial conformational equilibria in cyclohexane derivatives.[71]

R	X	% *endo* (at 25 °C)	$\Delta\Delta H^{\ddagger}$ (kcal mol^{-1})
H	COOH	80.2	0.65 ± 0.01
CH_3	COOH	29.2	-0.74 ± 0.01
H	CHO	74.4	0.57 ± 0.06
CH_3	CHO	17.0	-1.21 ±0.04
H	$COOCH_3$	74.3	0.56 ± 0.04
CH_3	$COOCH_3$	30.1	-0.25 ± 0.08

Table 1.3: *endo* Percentage and Relative Activation Enthalpy (*endo/exo*) of the Diels-Alder Reactions of Cyclopentadiene with Various Dienophiles

Apeloig and Matzner have conducted a theoretical study on the reactions of cyclopropene with numerous dienes.[72] In this study, the authors accredited the *endo/exo* selectivity to the presence of *SOI* in a LUMO diene–HOMO dienophile interaction. In an alternative theoretical investigation into the reactions of cyclopropene with open-chain dienes, it was demonstrated that the *endo/exo* selectivity can be accredited to an amalgamation of electron delocalization and electrostatic forces.[73] Another supportive explanation involves the existence of a destabilising interaction in the *exo* transition state. This culminates from the repulsion (due to electrostatic and/or van der Waals interactions) between a hydrogen atom of the methylene group of cyclopropene and the inner hydrogen atoms of butadiene (situated at a distance of 2.3 Å).

Figure 1.12: Alternative Interactions Proposed in Order to Explain the *endo* Preference Found in the Diels-Alder Reaction Between 1,3-Butadiene and Cyclopropene.

Furthermore, electrostatic forces have been ardent, here for example, the minor *endo* preferences calculated for the reactions of butadiene with simple *α,β*-unsaturated carbonyl compounds (such as acrolein[74] or methyl acrylate[75]) can be accredited to electrostatic repulsions. These occur in the *exo* transition states between the positive charges associated with the *"in"* hydrogens of butadiene and the carbonyl carbon of the dienophile (**Figure 1.13**). A further example of the influence of electrostatic interactions on the *endo/exo* selectivity of Diels-Alder reactions is the furan + cyclopropenone cycloaddition. Therefore, the high *exo* preference has been accredited to the existence of a potent electrostatic stabilization between the furan oxygen and the carbonyl carbon of cyclopropenone.[76]

Figure 1.13: The Influence of Electrostatic Interactions on the *endo/exo* Selectivity of Diels-Alder Reactions.

The importance of the dienophile transoid-cisoid conformational equilibrium in determining the *endo/exo* selectivity is emphasised by Mattay.[77] The transoid conformation is preferred in solution and is demonstrated to lead to *endo* product, however, the cisoid conformation (favoured in the gas phase) generates the *exo* adduct.

1.3.3. Solvent Effect on Diels−Alder Reactions

The effects of solvents on Diels–Alder reactions are well reported with studies focusing on the theoretical and experimental treatment of solvation effects on such reactions.[78] In a common approach, a particular property of a reaction (e.g. its rate or selectivity) is examined in a large variety of solvents. These solvents contain unique features, quantified by their physical properties (e.g. refractive index, dielectric constant) or empirical parameters.

A number of sources, when debating solvent effects on organic reactions, put forward the Diels-Alder cycloaddition as a common example of a reaction indifferent to the selection of a solvent. This characteristic is demonstrated by the data in **Table 1.4** which refers to the rate of dimerisation of cyclopentadiene **1.51**.

In this reaction, the second-order rate constants in a wide range of organic solvents are similar to each other and also to the rate constant in the absence of a solvent. The data in **Table 1.4** illustrates the very unique example of a Diels-Alder reaction between two purely hydrocarbon reactants. Typically, Diels-Alder reactions only occur at a substantial rate when either diene or dienophile is activated by an electron donating or withdrawing substituent. These substituents almost consistently comprise of heteroatoms. These atoms interact effectively with the solvent, causing an intensification of the solvent effect on the reaction. A large number of these processes have been examined; originally the correlation of the rate of Diels-Alder reactions with solvent parameters was reported in 1974.[79]

solvent / state	K_2 (M^{-1} s^{-1})
gas phase	$6.9 \cdot 10^{-7}$
Neat	$5.6 \cdot 10^{-7}$
Carbon tetrachloride	$7.9 \cdot 10^{-7}$
Nitrobenzene	$13 \cdot 10^{-7}$
Ethanol	$19 \cdot 10^{-7}$

Table 1.4: Second-Order Rate Constants k_2 for the Dimerisation of Cyclopentadiene in Solution and in the Gas Phase at 25 °C

Desimoni and Mayoral have reported comprehensive analyses of solvent effects on Diels-Alder reactions.[80] Initially, Desimoni supported the Acceptor Number (*AN*) as the prevailing

solvent parameter. Additional investigation exposed the rate constants for Diels-Alder reactions as not yielding satisfactory correlations with the *AN*.[81] These investigations demonstrated either reactions that were almost insensitive to solvent effects (like the dimerisation of cyclopentadiene, **Table 1.4**) or reactions that responded predominantly to the electron-pairdonor property of the solvent. As a result of these findings, the authors divided Diels-Alder reactions into three categories. In type I, the rate constants rise with increasing Lewis-acidic character of the solvent quantified by the *AN*. This behaviour mirrors LUMO solvent–HOMO solute interactions and is comparable to Lewis-acid catalysis. In type II, electron donation by the solvent through soft-soft interactions delays the reaction and HOMO solvent–LUMO solute interactions account for this observation. Type III comprises of Diels-Alder reactions which exhibit very slight solvent effects and are relatively indifferent to specific solute-solvent interactions.

The significance of solvent density in the unique case of intramolecular Diels-Alder reaction in extremely viscous media was demonstrated by Firestone *et al*.[82] An intriguing new medium for the Diels-Alder reaction was presented in 1990 by Grieco *et al*;[83] a 5 molar solution of lithium perchlorate in diethyl ether. The substantial accelerations of Diels-Alder reactions in this medium were accredited to a high internal pressure by Grieco and later also by Kumar.[84] This viewpoint has been questioned and alternative accounts put forward. In particular, Lewis-acid catalysis by the lithium cation has been presented[85] and efficient stabilisation of the Diels-Alder transition state by this extremely polar medium.[86] Faita *et al.*[87] have illustrated that only when Diels-Alder reactions are not responsive to Lewis-acid catalysis, internal pressure can account for the (in this case always modest) accelerations. Additionally, a valuation of the Lewis acidity of this ion in organic media has been published.[88]

The first to examine systematically the influence of the solvent on the *endo/exo* selectivity of the Diels-Alder reaction were Berson and co-workers.[89] The authors deduced the solvent reliance of the *endo/exo* ratio by considering the dissimilar polarities of the individual activated complexes involved. In the *endo* activated complex, the dipole moments of diene and dienophile are aligned, while in the *exo* activated complex they are facing in opposed directions. Therefore, the *endo* activated complex is of higher polarity than the *exo* activated complex and polar solvents diminish the preference for the formation of *endo* cycloadduct.

In some examples, solvent effects can be understood as the origin of the *endo* preference in solution. A common example of an *endo* preference incited by the effect of the medium is the cyclopentadiene + acrylonitrile reaction. Accordingly, experimental data for the reaction in

nonpolar solvents and approximations for the gas-phase cycloaddition suggest a very minor *exo* preference (by 0-0.4 kcal mol^{-1}). Remarkably, a correlation between the *endo/exo* ratio and solvent polarisability has been detected by Nakagawa and co-workers.[90] Consequently, an *endo* preference is identified when the reaction occurs in a large quantity of typical solvents. The Diels-Alder cycloaddition between acrylonitrile and piperylene manifests a behaviour pattern comparable to the analogous reaction with cyclopentadiene. Therefore, a preference for the *ortho-trans* adduct (corresponding to an *exo* approach) is identified in benzene solution, while the *ortho-cis* product (formed through an *endo* transition state) is favoured in polar solvents (e.g. methanol, ethanol, and acetone).

According to Mayoral *et al.*, the extensive multiparameter analyses indicated that a comprehensive report of the solvent effect on the *endo/exo* ratio requires numerous and differing interactions.[91,92,93,94] A significant contribution is hydrogen bonding by the solvent, additionally, solvent polarity and solvent solvophobicity are of importance.

1.3.4. Lewis-acid Catalysis of Diels-Alder Reactions

The catalysis of Diels-Alder reactions *via* formation of supramolecular assemblies is well established. Large molecules comprising of a cavity (e.g. cyclodextrins[95,96] or related basket[97] or capsule-like[98] structures) can bind both Diels-Alder reagents simultaneously and stimulate their reaction. Also, heterogeneous systems such as clays,[99] alumina[100] or silica gels[101] possess catalytic potential. Furthermore, catalysis by Brønsted acids,[102] Brønsted bases[103] and radicals[104] has established application in some special Diels-Alder reactions.

However, the most effective method by far is catalysis *via* Lewis-acids. In organic solvents, accelerations of the order of 10^4 to 10^6 supplemented by a significant increase in selectivity are not the exception. The striking effects that Lewis-acids apply on the rate of Diels-Alder reactions were identified by Yates and Eaton in 1960.[105] They examined the reaction between maleic anhydride and anthracene in the presence of aluminium trichloride. The reaction was completed in 1.5 minutes, whereas the estimated reaction time under equivalent conditions and in the absence of the catalyst was approximately 4800 hours. The FMO theory aids the understanding of the mechanism of activation by Lewis-acids. The electron withdrawing character of the catalyst lowers the energy of the LUMO of the reactant to which it is coordinated. As a result, the HOMO-LUMO energy difference decreases and in turn, the rate of the Diels-Alder reaction increases.

The influence of Lewis-acids on the selectivity was originally revealed by Sauer and Kredel in 1966.[106] The addition of $AlCl_3 \cdot OEt_2$ activated improvement of the *endo/exo* selectivity of the reaction between cyclopentadiene and methyl acrylate from 82% to 98% *endo*. The influences of Lewis-acids on selectivity can be granted by acknowledging one of the simplest dienophile-Lewis-acid complexes; protonated acrolein.[107]

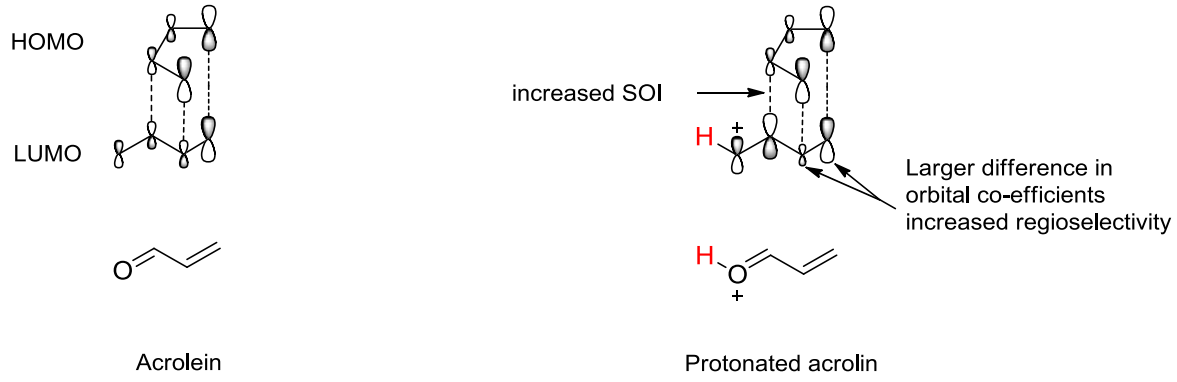
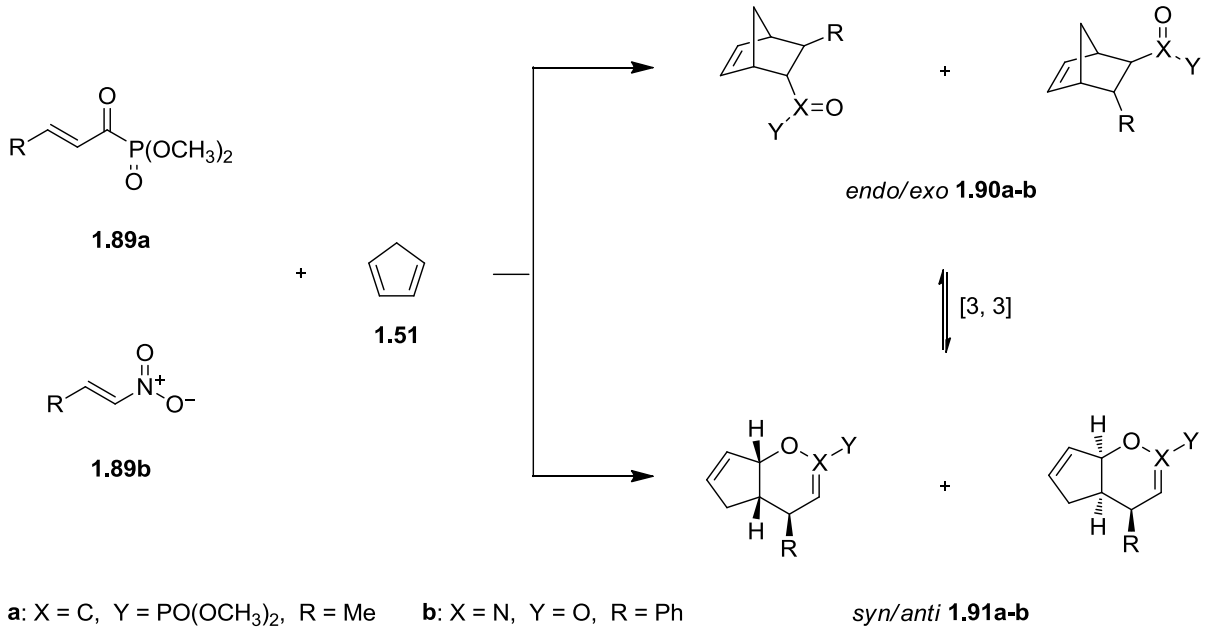


Figure 1.16: The Effect of Lewis-acids on Selectivity

In reference to FMO theory, the complexation of Lewis-acids to the dienophile or the protonation of the dienophile affects both the energy and orbital coefficients of carbon atoms of the LUMO of dienophile.[108] This interaction increases the coefficient in this orbital and as a result, improves the reactivity and stereoselectivity in comparison to their thermal equivalents. Generally, the *endo/exo* ratio is tightly controlled by selection of catalyst. For instance, cycloaddition of 1,3-bis(silyloxy)cyclohexadiene with chiral acrylamides, e.g., 1-[(*2R,5R*)-*trans*-bis(methoxymethyl)pyrrolidin-1-yl]-propenone demonstrated high *endo/exo* selectivity (4:1) when *tert*-butyldimethylsilyl triflate (TBSOTf) was applied as the catalyst. Furthermore, reversed selectivity is detected with 100% *exo* selectivity being achieved when $Eu(fod)_3$ catalyst is employed. Remarkably, the thermal reaction at 170 ºC was less selective with 1:3 *endo/exo* ratio being reached.[109] In the majority of cases, Lewis-acid catalysed cycloadditions are beneficially performed under extremely moderate conditions, often below 0 ºC which will often improve the diastereoselectivity.[110,111] Furthermore, the regioselectivity[112] and the diastereofacial selectivity[113] will increase in the presence of Lewis-acids.

The highly useful Diels-Alder reactions between dienes and heterodienes often yield two different pericyclic products. The experimental work of Denmark[114] and Hanessian[115] demonstrated that the reactions between crotonoyl phosphonates **1.89a** and nitroalkenes

1.89b with cyclopentadiene **1.51** can lead to combinations of Diels-Alder **1.90a-b** and hetero-Diels-Alder **1.91a-b** cycloadducts. In the thermal reactions, cyclopentadiene functions as a 4π component and primarily yields the *endo* and *exo* Diels-Alder cycloadducts, accompanied by minor quantities of the hetero-Diels-Alder cycloadducts (*anti* and *syn*). In the example of *trans*-phenylnitroethylene, the Diels-Alder cycloadduct is generated exclusively. Lewis-acids such as $SnCl_4$, reverse the periselectivity and cyclopentadiene now functions as the dienophile. The main products generated are the hetero-Diels-Alder cycloadducts with just minor quantities of Diels-Alder products.



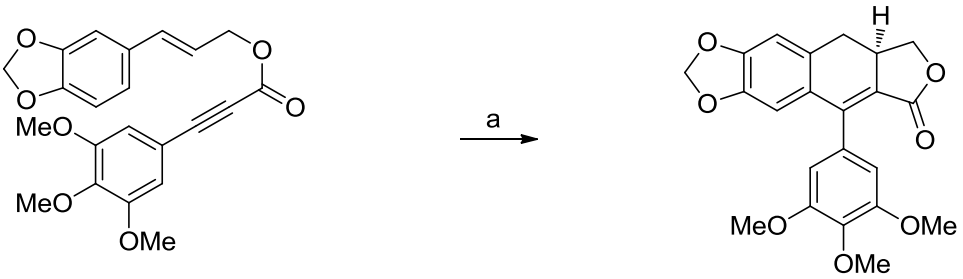
Scheme 1.15: Possible Diels-Alder and Hetero-Diels-Alder Reactions of Cyclopentadiene with **1.89a-b**

A number of Lewis-acids have been used in Diels-Alder reactions; however, the influence of a Lewis-acid on reaction outcome is not always advantageous and is highly substrate specific.[116] The majority of studies demonstrate that the appropriate Lewis-acid to use with a set of substrates is usually best determined by experimentation.

1.3.5. Intramolecular Diels-Alder Reactions

The [4+2] pericyclic reaction, as described by Diels and Alder, was originally examined in the context of the intermolecular reaction, concentrating on the stereospecific and

regiospecific combination of two distinct entities. In contrast, the intramolecular Diels-Alder (IMDA) reaction, where the diene is connected to the dienophile *via* a tether was not examined thoroughly until the 1960s. The initial application of the IMDA reaction in the context of natural product synthesis was reported in 1963, with the preparation of γ-apopicropodophyllin **1.93**.[117] The cinnamyl phenyl propiolate **1.92** was prepared *via* esterification of the respective *E*-cinnamyl alcohol and acid chloride. When **1.92** was subjected to vigorous conditions it culminated in the desired intramolecular cyclisation.



1.92 **1.93**

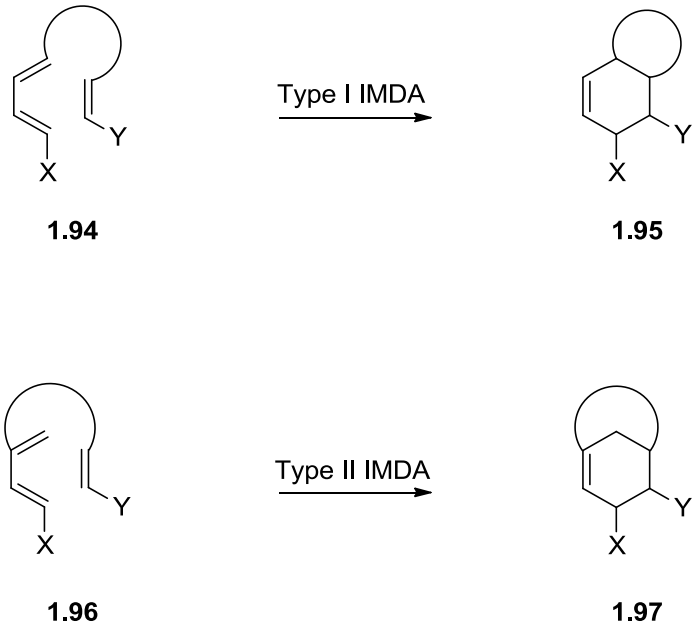
Reagents and Conditions: Ac_2O, heat, 48%.

Scheme 1.16: The Application of an IMDA to form γ-apopicropodophyllin **1.93**

The intramolecular form of the Diels-Alder reaction has numerous distinct benefits over the intermolecular form. The synthetic benefits of employing an intramolecular Diels-Alder reaction (IMDA) emerge from the finding that many of the limiting electronic and steric necessities of the intermolecular Diels-Alder reaction and the chemoselectivity and regioselectivity of the outcomes, can be positively altered using an intramolecularly tethered triene system. The example in **Scheme 1.16** demonstrates the high regioselectivity attainable in IMDA reactions, largely as a result of the torsional and geometric restrictions enforced by the dienophile tether.

The pre-organisation and orientation of the diene and dienophile reduces the entropy demands, relative to the analogous intermolecular reaction enabling the IMDA reaction to progress more easily. Furthermore, by including a stereocenter in the triene precursor, discernment between the diastereotopic faces of the diene and dienophile can be attained. The nature of the linking tether is also significant in effecting the rate of reaction. These benefits have led to the comprehensive use of the IMDA in total synthesis and these applications have been reviewed.[118,119]

The IMDA reaction can be defined as either type I or type II, although this is dependent on the position of attachment of the dienophile to the diene (**Scheme 1.17**).

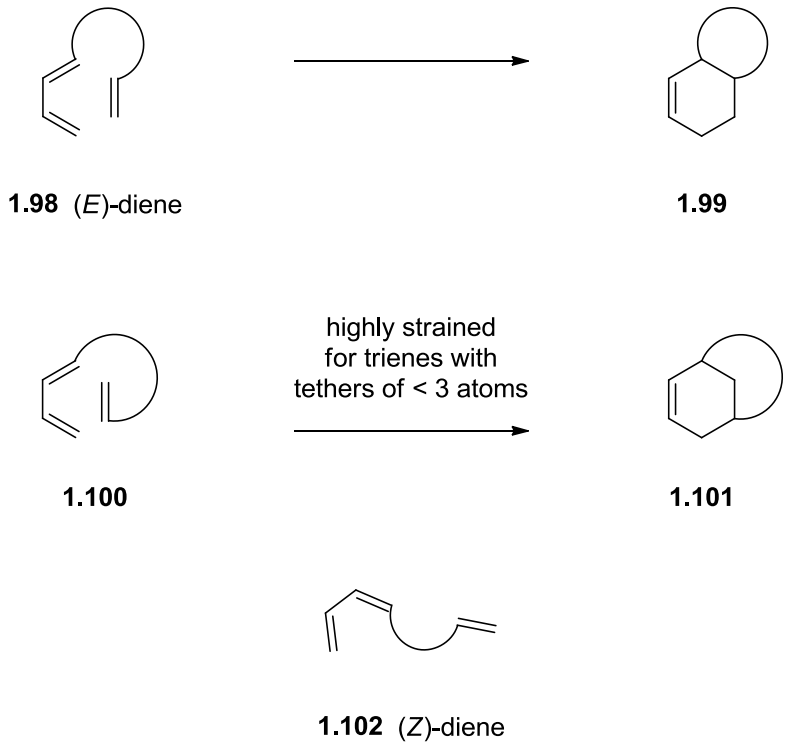


Scheme 1.17: Type I and Type II IMDA Connectivity and Products

The type I IMDA reaction, consisting of a C1 terminally attached diene and dienophile system **1.94**, forms a fused bicyclic ring system (bicyclo[n.4.0]alkene) **1.95** with a connective bond in common upon cyclisation. In the preparation of a variety of organic targets, type I reactions have been applied to excellent effect and are well reported.[120,121] In contrast, the type II IMDA reaction which exhibits C2 connectivity **1.96** and produces a bridged bicycle (bicyclo[n.3.1]alkene) **1.97** upon cyclisation, has been the subject of less synthetic investigation.[122] Predominantly, it has been demonstrated that both Type I and Type II IMDA reactions occur if the tether consists of three or more atoms. This is in account of the high level of strain present in the transition states of reactions of precursors with one or two atoms in the connecting chain.

The intramolecular Diels-Alder reaction does not typically suffer from the issue of regioselectivity that marks the intermolecular reaction. The attack of the dienophile (**Scheme 1.18**) is constrained by the length of the tether that joins the two reacting centres; the reaction of (*E*)-dienes **1.98** generate exclusively fused products **1.99** and not bridged products **1.101**.[123] Examples in the literature indicate that the reaction is more likely to form the bridged product if a (*Z*)-diene such as **1.102** is used[124] or if the tether connecting the two

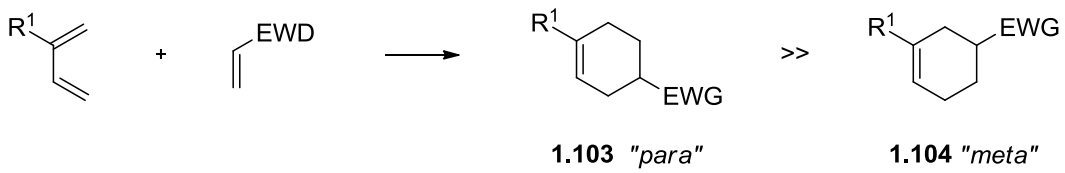
reacting centres is considerably long (greater than ten atoms).[125] However, the number of reactions that form bridged products remains a small minority of those that have been reported.



Scheme 1.18: Type I Intramolecular Diels-Alder Reactions

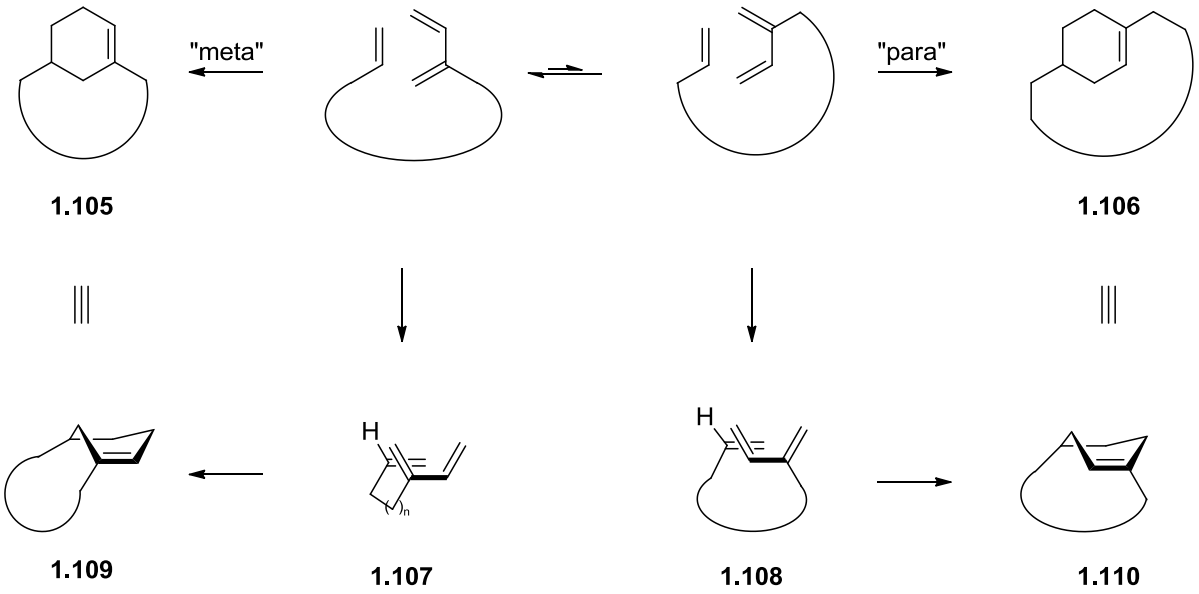
An inherent regiochemical bias favouring the 1,4-disubstituted product **1.103** over the 1,3-adduct **1.104** is exhibited by intermolecular Diels-Alder cyclisations of 2-substituted dienes and dienophiles with electronwithdrawing groups. This outcome is typically understood in terms of FMO theory, *via* the calculated orbital coefficients of the HOMO diene–LUMO dienophile interaction.[126] Alternatively, preference for the formation of the *meta*-cycloadduct **1.105** is demonstrated by type II IMDA reactions forming small bicyclic rings. This is partly on account of torsional and geometric strain acquired in meeting the requirements for the effective overlap interaction of the relevant orbitals (**1.107** vs **1.108**). In addition, it is also due to the *meta*-regioisomer **1.105** which consists of the transcycloalkene in the larger ring (**1.109** vs **1.110**) (vide infra) (**Figure 1.17**).[126]

Intermoleculer Diels-Alder



1.103 *"para"* **1.104** *"meta"*

Type II Intramolecular Diels-Alder



1.105 **1.106** **1.109** **1.107** **1.108** **1.110**

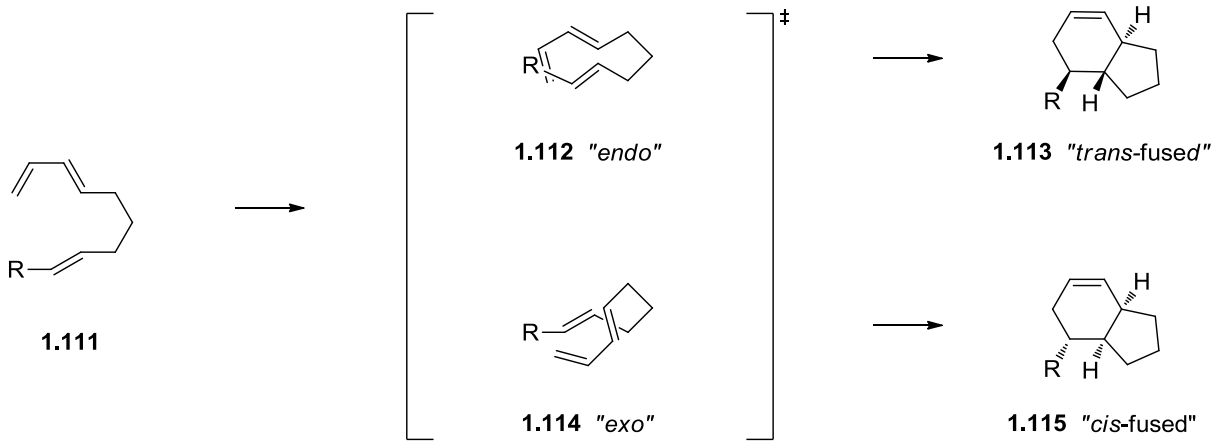
Figure 1.17: Formation of *meta*- and *para*-regioisomers

As the tether size increases, difference in energy between the *meta* and *para* isomers **1.105** and **1.106** decreases. Also, the IMDA cycloaddition is rapidly affected by the steric, conformational and electronic factors that influence intermolecular pericyclic reactions. If the tether consists of 3-5 atoms, the *meta* regioisomer is the selected product of cycloaddition irrespective of the dienophile's activation pattern and cyclisation method (thermal or Lewis-acid catalysis).[126]

The IMDA reaction is capable of stereoselectively generating up to four new contiguous stereocenters. The subject of stereoselectivity naturally takes place, as both *cis* and *trans*-fused cycloadducts are potential in the example of (*E*)-diene, the most commonly observed class of substrates.[127] In the case of substrates **1.111** and **1.116** in the IMDA reaction leading

to [4.3.0] and [4.4.0] systems, two transition states (*endo* and *exo*) are possible. The *cis*-fused products are resultant from the *exo* mode of cycloaddition and the *endo* transition state of **1.111** and **1.116** induces *trans*-fused bicycles. In the [4.4.0] system, a chair-like transition state is typically suggested.

Bicyclo[4.3.0]system



Bicyclo[4.4.0]system

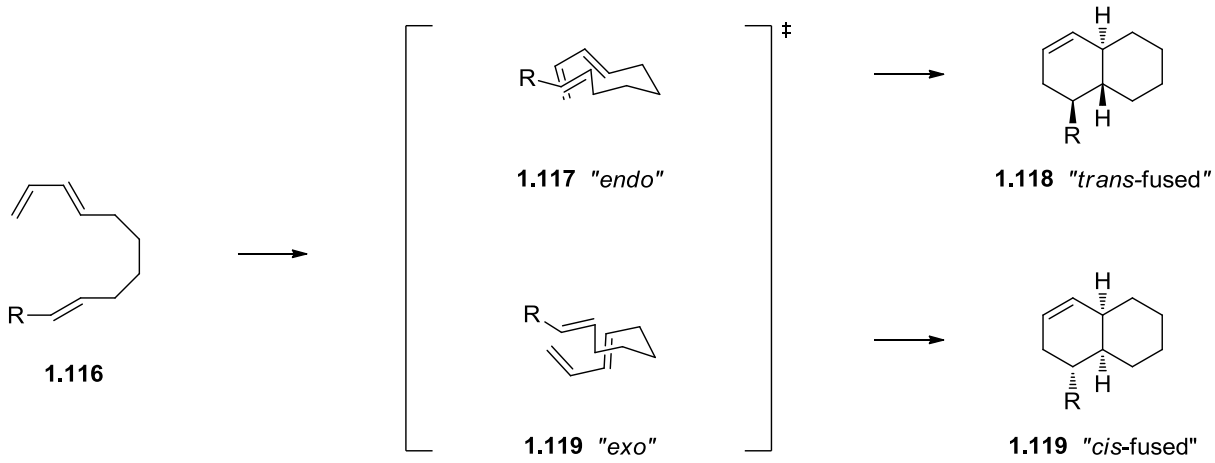
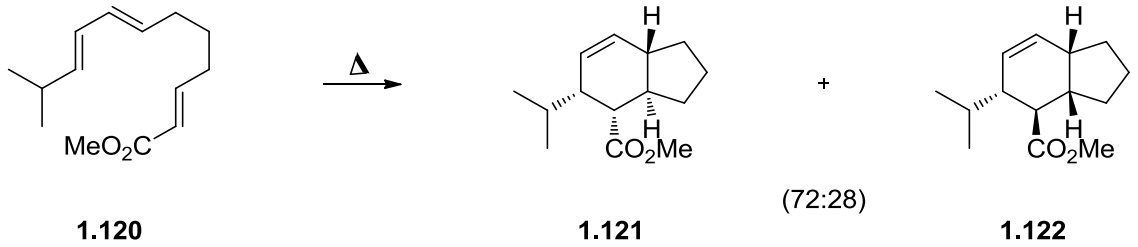


Figure 1.18: *endo* and *exo* Transition States for the [4+2] Reaction of **1.111** and **1.116** Leading to Bicyclo[4.3.0] and [4.4.0]systems

In the bicyclo[4.3.0]system, *cis*-fused cycloadducts normally dominate in the thermal cyclisation of unsubstituted trienes.[128] However, if substituted, *trans*-fused products

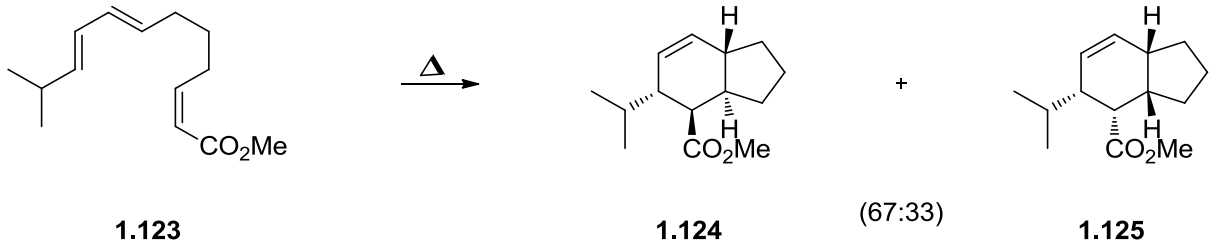
originating from the *endo* mode of addition usually prevail. The example in **Scheme 1.19** illustrates this, in which the reaction of **1.120** preferentially generates **1.121** over **1.122**.[129]



1.120 **1.121** **1.122**

Scheme 1.19: IMDA Reaction of **1.120** Preferentially Generates **1.121** over **1.122**

Although this reaction does externally conform to the *Alder endo* rule, the selectivity is unexpectedly low. Indeed, there are a number of reactions that completely disregard the *endo* rule such as the isomer of ester **1.120** with the dienophile in the *Z*-form, as illustrated in **Scheme 1.20**.



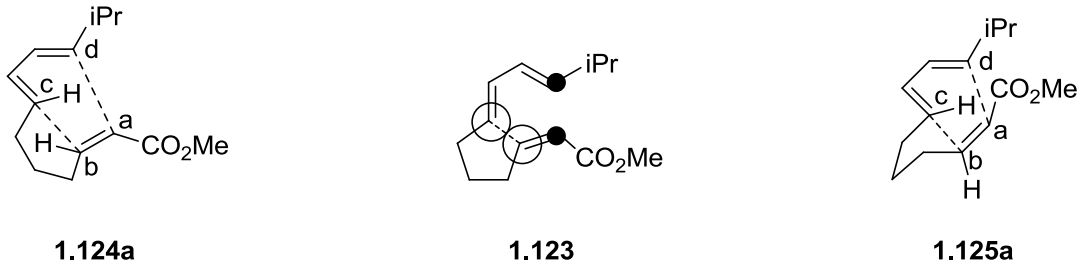
1.123 **1.124** **1.125**

Scheme 1.20: IMDA Reaction of **1.123** Preferentially Generates **1.124** over **1.125**

In reference to the *endo* rule, ester **1.123** is expected to yield *cis*-hydrindene **1.125** but the dominant form is *trans*-hydrindene **1.124**. It is understood that this and a number of other reactions do not adhere to the *endo* rule because of asynchronous bond formation.[130] Although the Diels-Alder reaction forms both bonds in a concerted manner; they are frequently generated at considerably different rates. In an intramolecular Diels-Alder reaction with a tether connecting the two reacting centres less than four atoms long, it has been calculated that synchronous bond formation is not likely because of the restrictive nature of the tether.[131]

According to FMO theory, the most progressive bond formation in a concerted reaction of this kind will be between the termini of the diene and dienophile that contain the highest

orbital coefficients. The coefficient at Cb is higher than at Ca and the coefficient at Cc is higher than at Cd in ester **1.123** (**Figure 1.19**, with orbital coefficients shown in plain view). As a result, the bond formation between Cb and Cc (indicated with a dotted line) is significantly more progressive than between Ca and Cd.



1.124a **1.123** **1.125a**

Figure 1.19: Orbital Coefficients of **1.123** (Shown in Plain View)

Transition state **1.125a** illustrates that to form *cis*-hydrindene **1.125** (with reference to the *endo* rule), the two carbon chains on Cb and Cc in the cyclopentane ring need to be eclipsed, which does not occur in **1.124a**. It is probable that the energy of the staggered configuration of transition state **1.124a** will be significantly lower than that of the eclipsed transition state **1.125a**. Therefore, in transition state **1.124a** the more advanced bond forms more readily, culminating in compound **1.124** being preferentially formed.

The origins of stereoselectivity in the intermolecular Diels-Alder reaction are generally accounted for by *Secondary Orbital Interactions* between the diene and dienophile. Despite being usually less than several kcal mol^{-1} in magnitude, the outcome of these interactions is the dominant formation of the *endo* adduct under kinetic control.[132] Type II IMDA reactions demonstrate total stereoselectivity with cycloaddition occurring from a conformation where the tether occupies the *endo* position **1.127**. The reduction of torsional strain energy related with the *exo* tether **1.130** controls support from *Secondary Orbital Interactions* (**Figure 1.20**) affording an "*out*"-bridging adduct **1.128**.

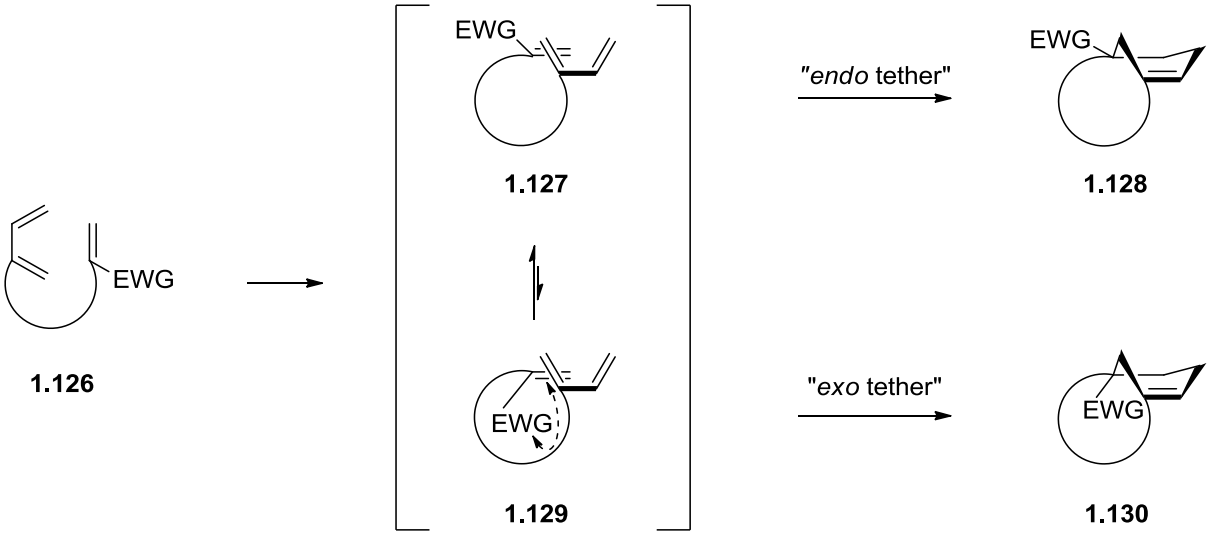
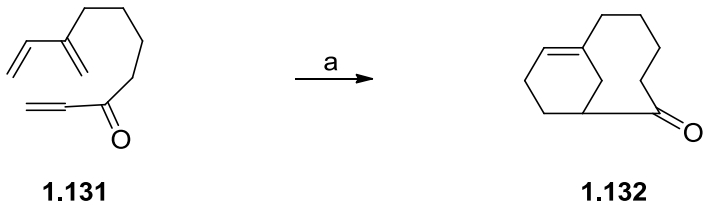


Figure 1.20: Stereoselectivity in Type II IMDA Reactions

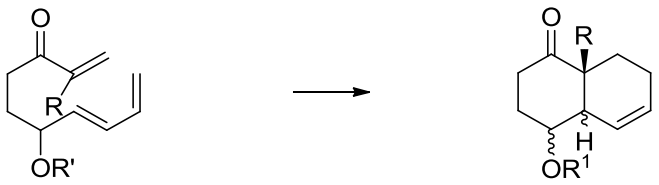
Similar to intermolecular Diels-Alder reactions, the IMDA reactions are catalysed by Lewis-acids. A moderate method for the synthesis of bicyclco[n.3.1] bridgehead alkenes by Lewis-acid catalysed IMDA cycloadditions, has been reported by Shea and Gilmanl.[133] Intramolecular cycloaddition of **1.131** in methylene chloride comprising of diethylaIuminium chloride at 21 °C for 2 hours, yielded bicycloundecenone **1.132** (**Scheme 1.21**).



Reagents and Conditions: (a) CH_2Cl_2, Et_2AlCl, 21 °C, 2h.

Scheme 1.21: Lewis-acid Catalysed IMDA reaction of **1.131**

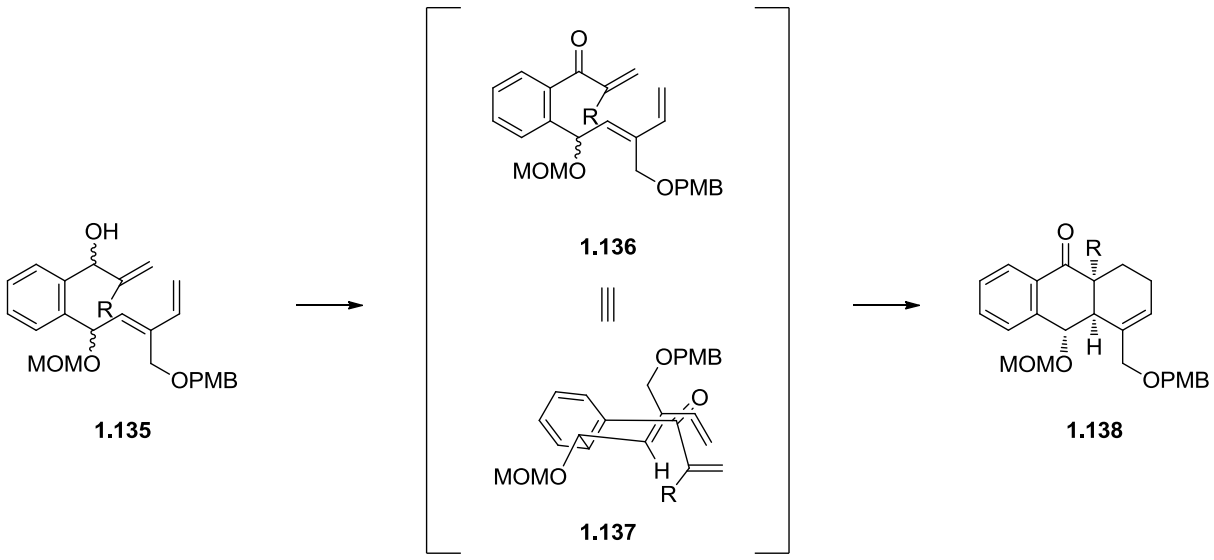
However, IMDA reactions do not always supply the optimum levels of stereoselectivity and reactivity. As illustrated in **Scheme 1.22**, triens like **1.133**, typically need high reaction temperature, long reaction times and produce complex mixtures of cycloadducts.[134,135]



1.133 **1.134**

Scheme 1.22: IMDA Reaction with no tether-Control Group

In order to enhance the cyclisation of substituted trienes in IMDA reactions, the enforcement of a conformational constraint on the molecule by the inclusion of a planar moiety such as an aromatic ring[136] or isopropylidene acetals[137] should be effective. The diene and the dienophile would both hold closer *via* the limited flexibility of the tether, thus enhancing the interactions in the transition state. As a result, these interactions would enable the IMDA reaction based on entropic grounds.



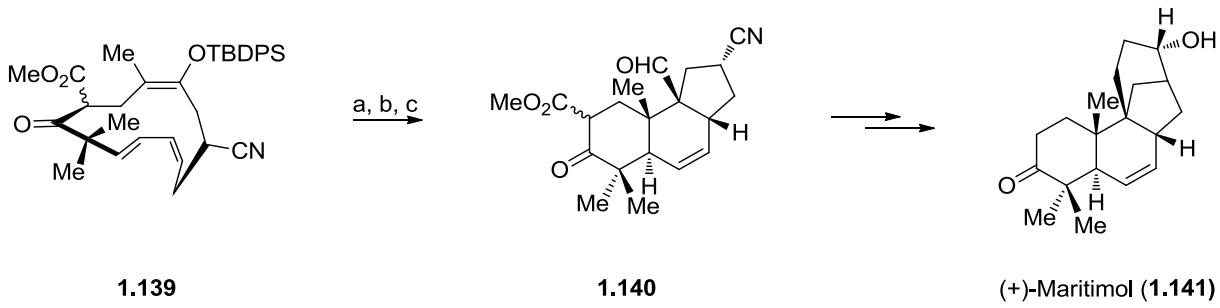
Scheme 1.23: IMDA with Planar Aromatic tether-Control Group

The aromatic ring moiety has been installed by Fallis and co-workers, with the aim of synthesising Taxol® analogues (**Scheme 1.23**).[140] Upon mild heating during an oxidation reaction, the reaction occurs spontaneously.

1.3.6. Transannular Diels-Alder (TADA) Reactions

The most frequent studies on the TADA reaction has been with 13-, 14- and 15-membered macrocycles under thermolytic reaction conditions. In addition, research on the effects of Lewis-acids and high pressures has been applied to the TADA reaction. The vigorous thermolytic conditions (200 °C to over 300 °C) occasionally employed, incite competitive [1,5] hydrogen shifts. This yields new dienes which can also undergo the TADA reaction and produce complex mixtures of cycloadducts. The utility of Lewis-acid catalysis is advantageous as the considerably lower temperatures constrain the hydrogen shifts and do not promote Alder-ene rearrangements of the C=C enophiles.[138,139]

An enduring synthetic challenge, with a unique tetracyclic stemodane framework and 10 stereocentres is the (+)-Maritimol **1.141**. The first asymmetric synthesis was reported by Deslongchamps *et al.*[140] and utilised a TADA reaction as a key step in the retrosynthetic analysis. Applying the group's previous skill in this area, it was predicted that the synthesis of maritimol would include stereospecific transformation of a 13-membered *trans-cis-cis*-(TCC)-macrocyclic triene **1.139**. Triene **1.139** was estimated to undergo cyclisation to yield the *trans-syn-cis*-(TSC)-ring system identified in the natural product.



1.139 **1.140** (+)-Maritimol (**1.141**)

Reagents and Conditions: a) Me_2AlCl, CH_2Cl_2, 75%; b) *p*-TSA; c) Dess-Martin.

Scheme 1.24: Syntehsis (+)-Maritimol **1.141** by Deslongchamps *et al.*[140]

It is evident that the TADA approach allows a considerably high increase in molecular complexity during the process of macrocyclisation and succeeding cycloaddition. Furthermore, this is only dependant on the ease of stereoselective triene macrocycle synthesis.

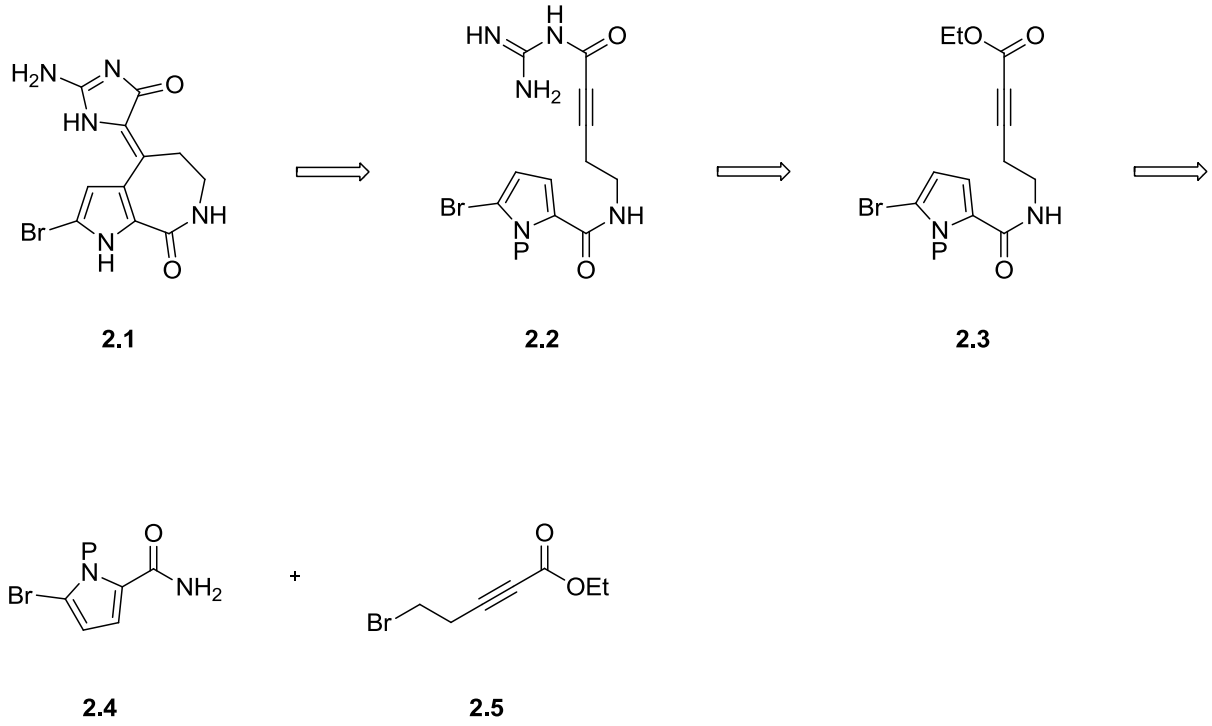
Chapter 2.

Results & Discussion

2.1.1. Previous Work and Overview of the Investigation

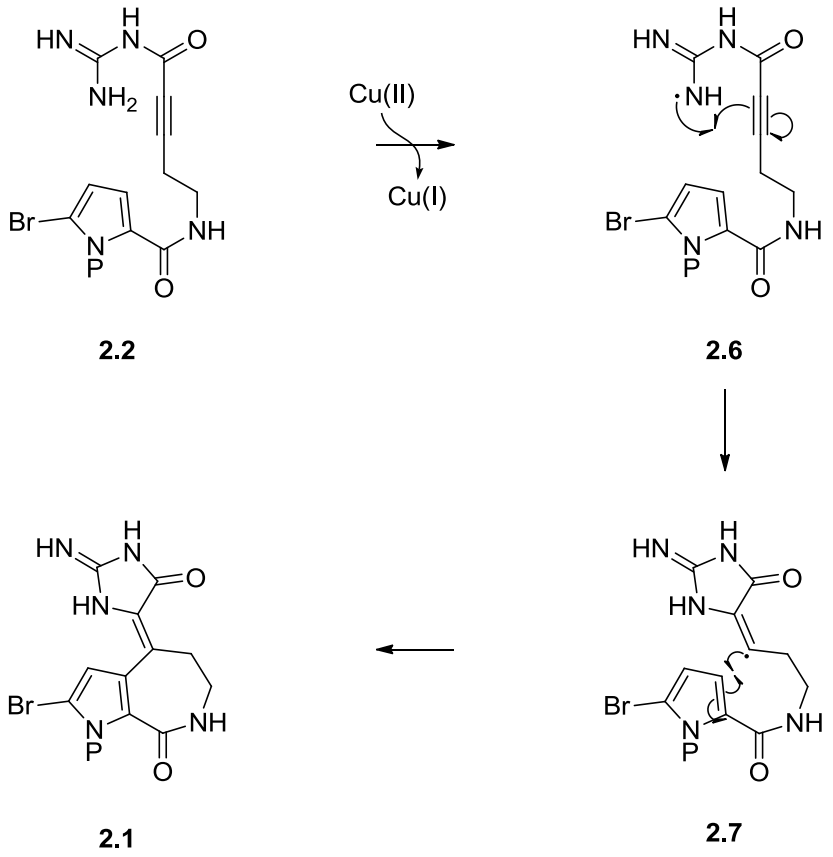
2.1.2. Previous Work

Hymenialdisine **2.1** is a metabolite isolated from the marine sponge *Stylissa Massa*.[141] It exhibits potent activity against murine P388 lympocytic leukaemia.[142,143] The Parsons' research group has been interested in the total synthesis of hymenialdisine **2.1** for some years.[144] The chosen retrosynthetic analysis for the synthesis of hymenialdisine **2.1** is shown below in **Scheme 2.1**.



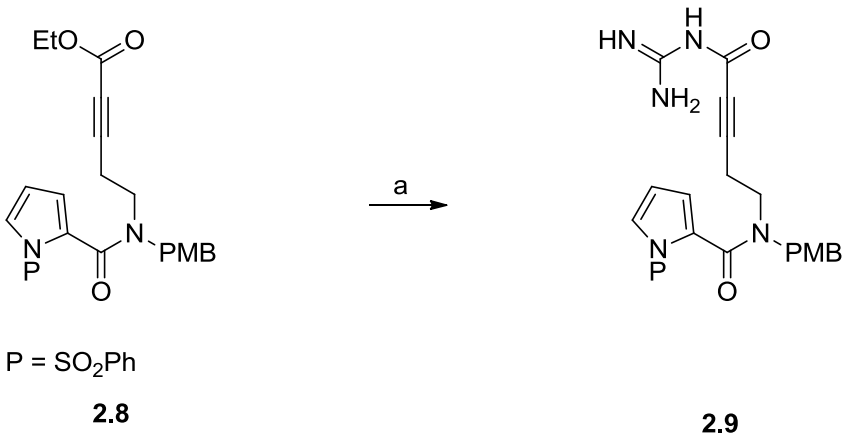
Scheme 2.1: Retrosynthetic Analysis of Hymenialdisine **2.1**

It was envisaged that the tricyclic hymenialdisine **2.1** could be formed from precursor **2.2** using a tandem radical cyclisation reaction as outlined in **Scheme 2.2**. Reaction of the electron-rich guanidine portion of precursor **2.2** with copper(II) salts was expected to generate a guanidinium radical **2.6**. This radical could then react with the proximal alkyne to afford an alkenic radical **2.7**. In turn, this alkenic radical could react with the pyrrole ring to afford the hymenialdisine **2.1**.



Scheme 2.2: Tandem Radical Cyclisation

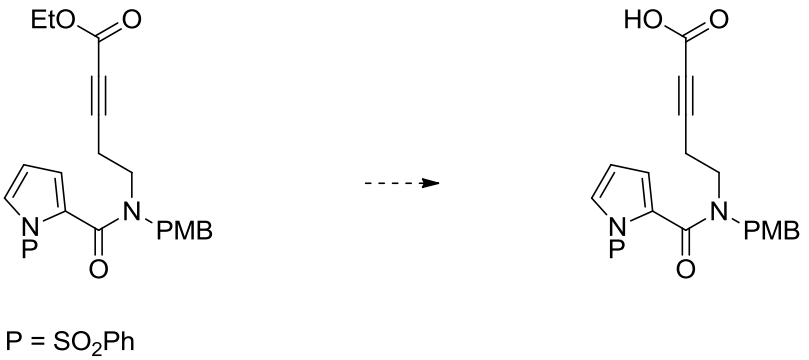
The ethyl ester **2.8** was constructed with the aim of forming the cyclisation precursor **2.2**. Subsequently, direct coupling of the ethyl ester **2.8** with the guanidine hydrochloride using sodium methoxide was attempted. This is outlined in **Scheme 2.3** below.



Reagents and Conditions: (a) NaOMe, guanidine hydrochloride, MeOH, 50 °C, 48h.

Scheme 2.3: Attempted Coupling of Ethyl Ester **2.8** with Guanidine

Unfortunately, none of the required product was isolated from this reaction. However, the coupling of carboxylic acid with guanidine using CDI was proposed. In order to test this reaction, several attempts were made to convert the ethyl ester **2.8** to the corresponding carboxylic acid **2.10**.



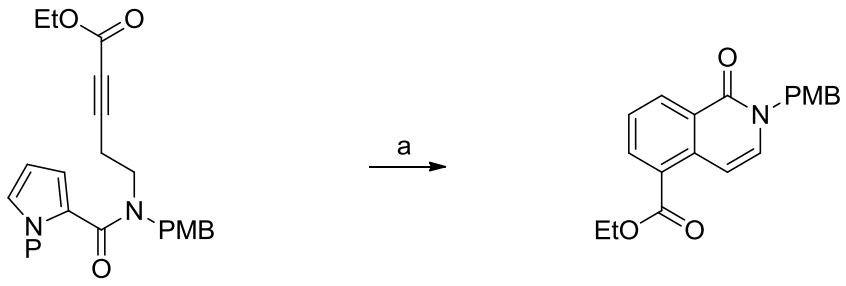
P = SO_2Ph

2.8 **2.10**

Scheme 2.4: Attempted Synthesis of Carboxylic Acid **2.10**

The saponification reaction was attempted with both KOH and LiOH in methanol. However, in both cases none of the required acid was isolated. The use of TMSOH in THF was attempted as a milder method of saponification. Unfortunately, none of the carboxylic acid was isolated. An acid catalysed saponification was also attempted but the yield of the required carboxylic acid was low (16%).

When ethyl ester **2.8** was treated with lithium iodide in refluxing pyridine the isoquinolin-1(*2H*)-one **2.11** was obtained in 48% yield as outlined in **Scheme 2.5**.



2.8 **2.11**

Reagent and Conditions: (a) LiI, pyridine, reflux, 16h, 48%.

Scheme 2.5: Synthesis of Isoquinolin-1(*2H*)-one Derivative **2.11**

The unexpected product was formed cleanly, no other products were observed by TLC analysis. The structure of isoquinolin-1(*2H*)-one **2.11** was originally deduced using NMR analysis and mass spectroscopy. However, as isoquinolin-1(*2H*)-one **2.11** was a solid it was possible to obtain a crystal structure which confirmed the proposed structure as shown in **Figure 2.1**.

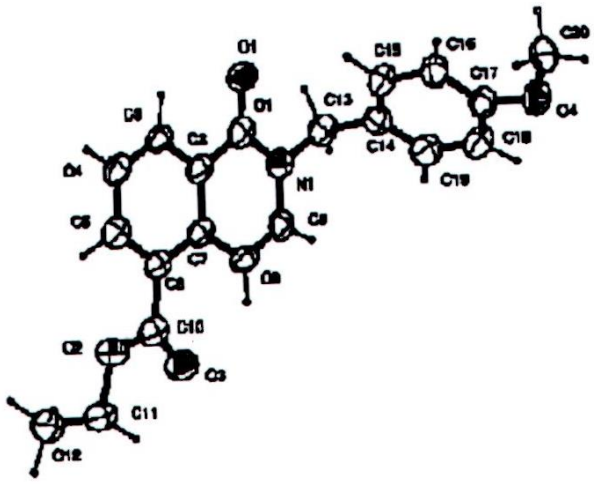
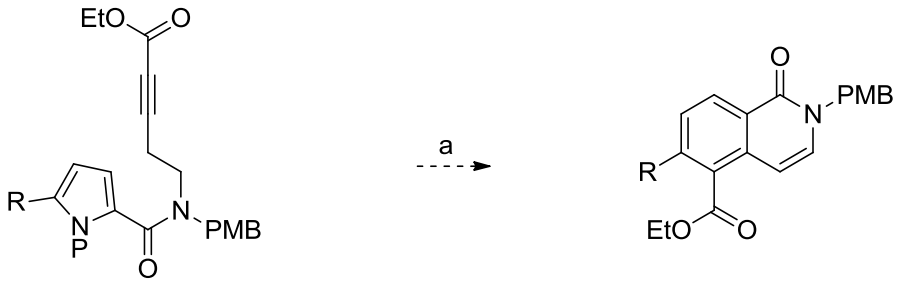


Figure 2.1: Crystal Structure of Isoquinolin-1(*2H*)-one **2.11**

2.1.3. Overview of the Investigation

It has been shown that the reaction of ethyl ester **2.8** with lithium iodide in pyridine afforded isoquinolin-1(*2H*)-one **2.11** in moderate yield (48%). Firstly, the aim of this project was to test if a cyclisation reaction with substituted pyrrole rings **2.12** is a viable option.

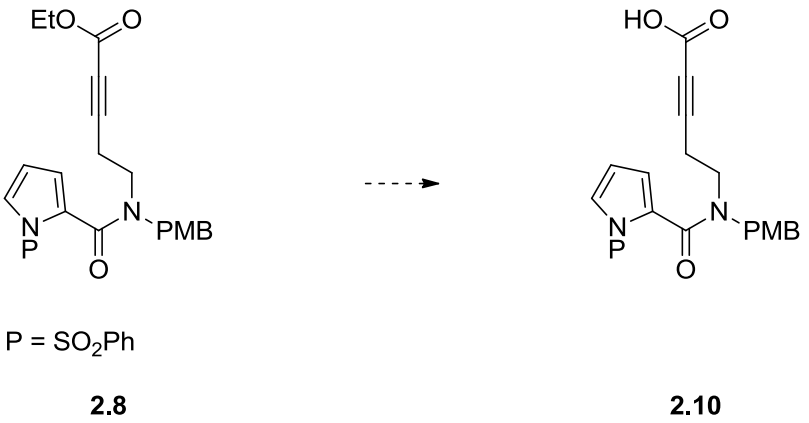


2.12 **2.13**

Reagent and Conditions: (a) LiI, pyridine, reflux.

Scheme 2.6: Generalised Substrate for the Investigation of Cyclisation Reactions

Previous work in the Parsons group developed a robust route to an advanced intermediate in the synthesis of hymenialdisine **2.1**. However, further steps were required to achieve formation of the desired cyclisation precursor **2.2** for the key tandem cyclisation. Subsequent work aimed to find a new route for the synthesis of carboxylic acid **2.10**.

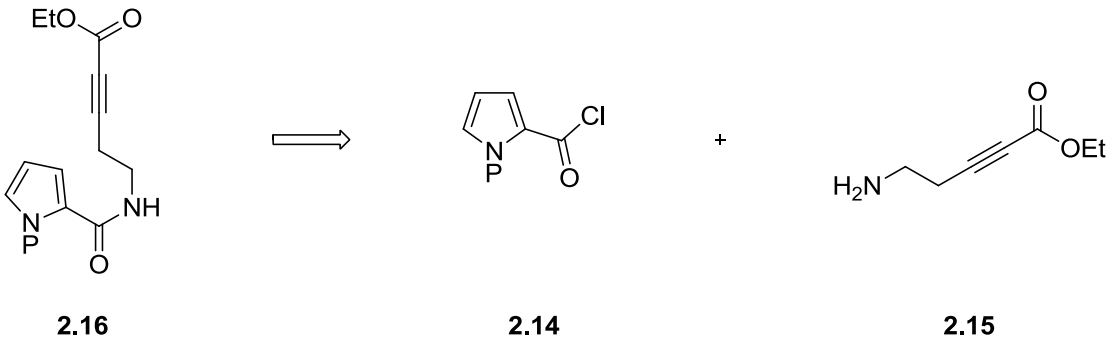


Scheme 2.7: Formation of Carboxylic Acid **2.10**

2.2. Synthesis of Isoquinolin-1(*2H*)-one 2.11

2.2.1. New Route for Synthesis of Ethyl Ester 2.8

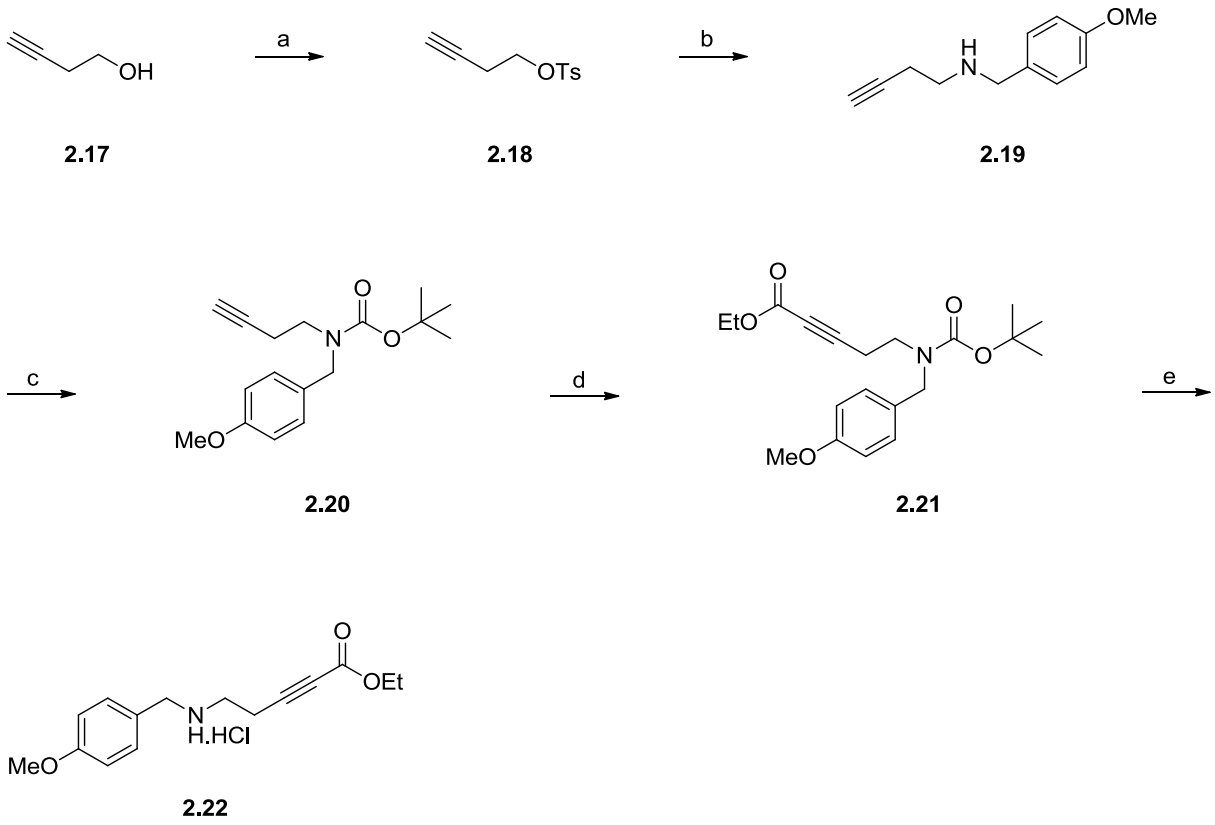
Previously, the Parsons' research group focused on the synthesis of amide **2.4** and bromide **2.5** which could then be coupled (**Scheme 2.1**). However, difficulties were encountered therefore a different route was proposed. Instead, it was suggested that the advanced intermediate **2.16** could be formed by coupling the acid chloride **2.14** with amine **2.15**.



Scheme 2.8: Revised Synthesis of Ethyl Ester **2.16**

2.2.1.1. *Synthesis of Amine Fragment 2.22*

The first task was the synthesis of amine fragment **2.22**. The synthesis of this fragment was based on the reported synthesis of a similar molecule by Fuerstner *et al.*[145] The synthesis of amine fragment **2.22** is outlined in **Scheme 2.9** below.



Reagent and Conditions: (a) TsCl, pyridine, $CHCl_3$, 0 °C to rt, 16h, 90%; (b) NaI, DMSO, 4-methoxybenzylamine, rt, 16h, 83%; (c) Di-*tert*-butyl dicarbonate, pyridine, CH_2Cl_2, 0 °C to rt, 16h, 97%; (d) *n*-BuLi, THF then ethyl chloroformate, -78 °C to rt, 16h, 80%; (e) 4M HCl in dioxane, CH_2Cl_2, 0 °C to rt, 4h, 95%.

Scheme 2.9: Synthesis of Amine Fragment **2.22**

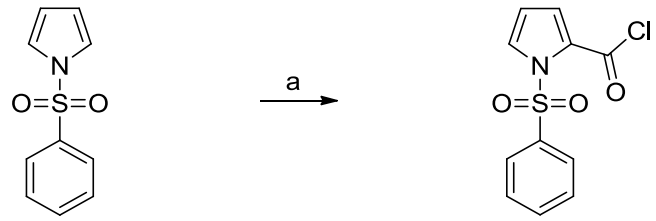
The first step involved the protection of 3-butyn-1-ol **2.17** with *para*-toluenesulfonyl chloride to produce the corresponding tosylate **2.18** (90% yield). The tosylate moiety was then displaced using 4-methoxybenzylamine and catalytic sodium iodide to afford amine **2.19** in 83% yield. Boc protection of amine **2.19** was then carried out prior to the reaction of the substrate with *n*-BuLi and ethylchloroformate. The yield of this alkylation step was found to be variable and several issues were encountered in obtaining a good yield. For example, the

n-BuLi must be freshly titrated. The order of addition of the reagents was also important. *n*-BuLi was added to a solution of alkyne **2.20** in THF at -78 °C under nitrogen. This cooled solution was then added drop-wise (*via* cannula) to a flask containing an excess of neat ethyl chloroformate at -78 °C under nitrogen. In general, the more slowly the anion solution was added to the ethyl chloroformate the greater the yield (addition times over 2 hours).

Initial attempts at *N*-Boc deprotection utilised trifluoroacetic acid in dichloromethane.[146] Although this method was effective on a small scale (83%), on a large scale the required product was not isolated. Indeed, TLC indicated that the free amine isolated on a small scale was decomposing over time, presumably due to the 1,4-addition taking place within the sample. To overcome this problem it was decided that HCl in dioxane should be used to deprotect the *N*-Boc group.[147] This would afford the required product as the HCl salt and would avoid the possibility of intermolecular 1,4-addition. This method afforded the required HCl salt **2.22** as a stable white solid in excellent yield (95%).

2.2.1.2. *Synthesis of Acyl Chloride 2.24*

The next step was to couple amine fragment **2.22** to the required acyl chloride **2.24**. Formation of the acyl chloride **2.24** was carried out as detailed by Kakushima *et al.* [148]using $AlCl_3$ and oxalyl chloride.



2.23 **2.24**

Reagent and Conditions: (a) $AlCl_3$, $(COCl)_2$, DCE, 0 °C to rt, 6h, 95%.

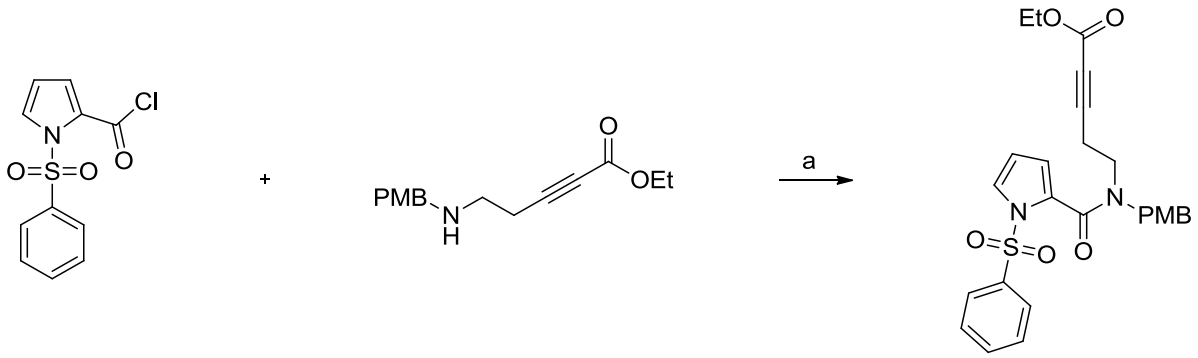
Scheme 2.10: Formation of the Acyl Chloride **2.24**

In this acylation reaction, oxalyl chloride was added drop-wise to a stirring suspension of $AlCl_3$ in DCE at 0 °C. After 20 minutes a solution of phenylsulfonyl pyrrole **2.23** in DCE was added. The reaction was quenched with ice-water and the product extracted into diethyl ether.

The required acyl chloride **2.24** was isolated as a brown oil (95%) which was used directly in the next step without further purification.

2.2.1.3. *Amide Coupling*

Once the amine **2.22** and acyl chloride **2.24** fragments were in hand, it was possible to attempt the coupling reaction. The amine salt **2.22** was first treated with saturated aqueous $NaHCO_3$ solution to afford the corresponding free base **2.25**. Amino ester **2.25** was then reacted with the acyl chloride **2.24** to produce the amide **2.8**.



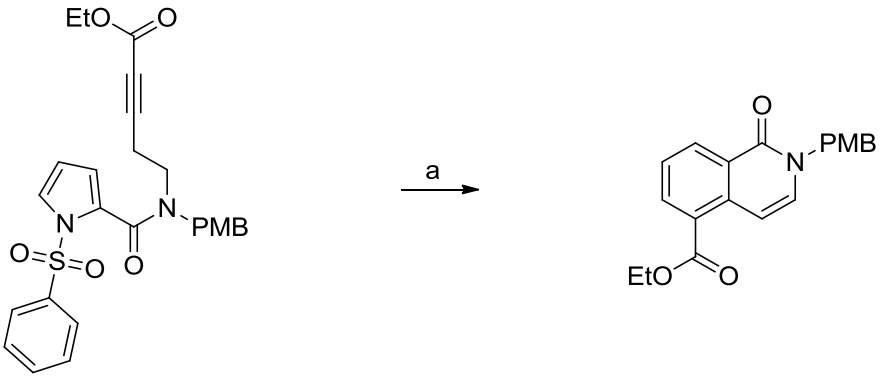
2.24 **2.25** **2.8**

Reagent and Conditions: (a) Et_3N, CH_2Cl_2, 0 °C to rt, 8h, 90%.

Scheme 2.11: Amide Coupling

2.2.1.4. *Investigation into the Role of LiI in the Cyclisation*

When ethyl ester **2.8** was treated with lithium iodide in refluxing pyridine the isoquinolin-1(*2H*)-one **2.11** was obtained in 52% yield as outlined in **Scheme 2.12**. Prolonging the reaction time up to 48 hours did not affect the yield.



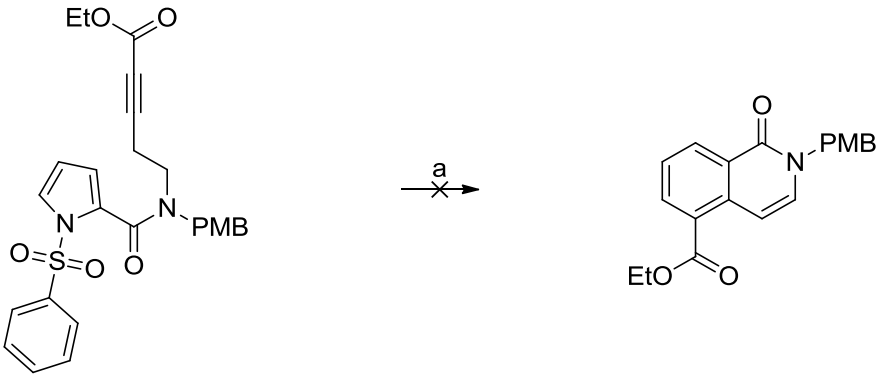
2.8 **2.11**

Reagent and Conditions: (a) LiI, pyridine, reflux, 16h, 52%.

Scheme 2.12: Synthesis of Isoquinolin-1(*2H*)-one Derivative **2.11**

The expected product was formed cleanly, no other products were observed by TLC analysis. The structure of isoquinolin-1(*2H*)-one **2.11** was deduced using NMR analysis and mass spectroscopy.

Following this result an investigation into the role of lithium iodide in the cyclisation reaction was carried out.



2.8 **2.11**

Reagents and Conditions: (a) Solvent, time, yield, see **Table 2.1**.

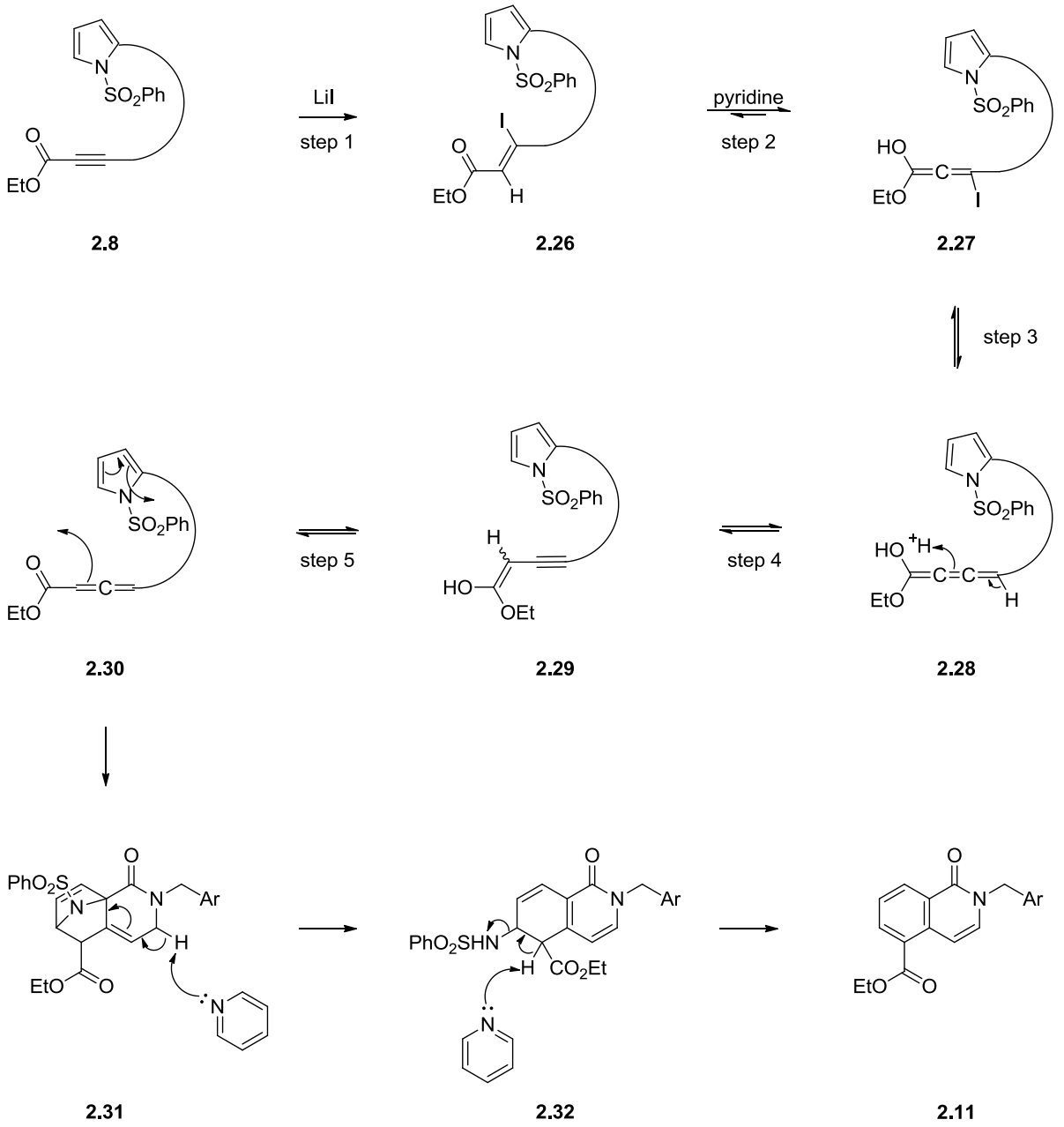
Scheme 2.13: Investigation into the Role of Lithium Iodide

The first experiment conducted, simply omitted the lithium iodide to observe what effect this had on the product of the reaction. Upon refluxing **2.8** in anhydrous pyridine for 24 hours, no reaction took place and all of ethyl ester **2.8** was recovered. Refluxing **2.8** in toluene for 24

hours in the absence of lithium iodide also failed to yield the desired compound. These reactions demonstrated that the lithium iodide is necessary for the formation of the isoquinolin-1(*2H*)-one **2.11**.

2.2.1.5. *Proposed Mechanisms for the Cyclisation*

On the basis of these results, plausible reaction mechanisms that are consistent with our experimental data are depicted in **Scheme 2.14a-b**.

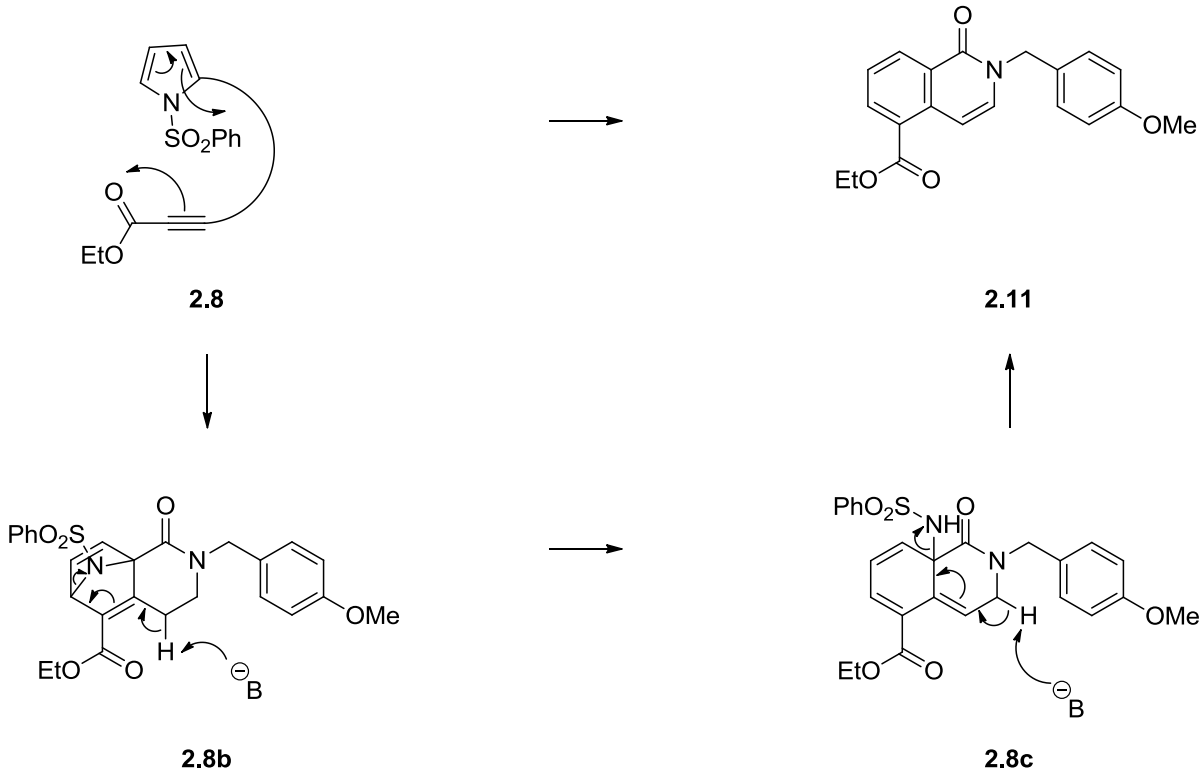


Scheme 2.14a: First Proposed Mechanism for the Novel Cyclisation

LiI might react with acetylenic ester **2.8** (step 1) to yield the desired *β*-iodovinyl ester **2.26**. The preferential α-vinyl enolisation (step 2) of **2.26** using mild base pyridine, provides an allenol **2.27** that subsequently undergoes elimination through an allylic C(sp^3)-H deprotonation (step 3) to cumulenol **2.28**.[149] The pyridine-promoted isomerisation of cumulenol **2.28** leads to the formation of alkynyl enol(ate) **2.29** which can protonate to allenyl ester **2.30**.[149] The next step is the intramolecular Diels-Alder reaction between the pyrrole and the allenyl ester moiety to afford the tricyclic intermediate **2.31**. Removal of an allylic proton by base affords intermediate **2.32**. Removal of second proton instigates the loss of the electron withdrawing phenylsulfonyl amine group and results in the formation of **2.11**.

Base-mediated 1,2-eliminations to produce allenes, a significant pathway to unsaturated hydrocarbons, have been previously investigated.[150] For those allenes that have been obtained from elimination reactions of vinyl halides, the presence of strong bases such as LDA and LiHMDS is necessary. The presence of strong bases could pose a problem in terms of functional group tolerance in the synthesis of functionalised allenes. Remarkably, the employment of mild organic base pyridine provided an allenyl ester which underwent intramolecular Diels-Alder reaction to form isoquinolin-1(*2H*)-one **2.11** (**Scheme 2.12**).

The second proposed mechanism for the novel cyclisation is shown below in **Scheme 2.14b**.

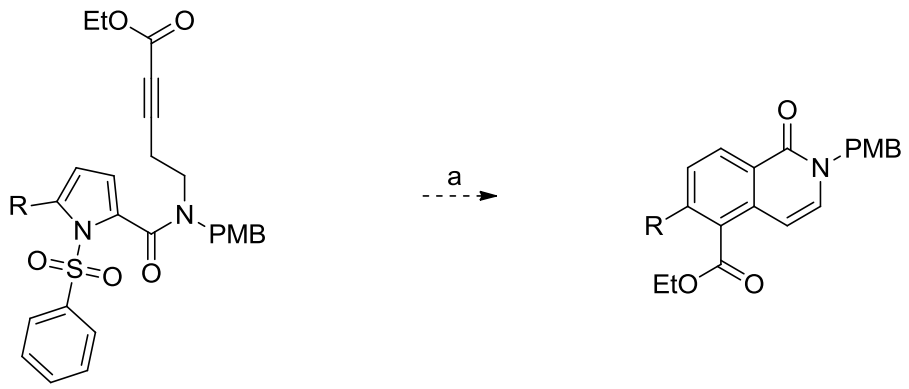


Scheme 2.14b: The Proposed Mechanism for the Novel Cyclisation

The first step is the intramolecular Diels-Alder reaction between the pyrrole and the alkyne moiety to afford the tricyclic intermediate **2.8b**.[51] Removal of an allylic proton affords intermediate **2.8c**. Removal of second proton instigates the loss of the electron withdrawing phenylsulfonyl amine group and results in the formation of **2.11**. The driving force for this reaction is the formation of the stable aromatic ring.

2.3. Synthesis of Various Diels-Alder Products

It has been shown that the reaction of ethyl ester **2.8** with lithium iodide in pyridine afforded isoquinolin-1(*2H*)-one **2.11** in moderate yield (52%). Our target was to develop this IMDA reaction by using a series of precursors with substituted pyrrole rings **2.33** which should afford the corresponding isoquinolin-1(*2H*)-ones **2.34** as shown below in **Scheme 2.15**.



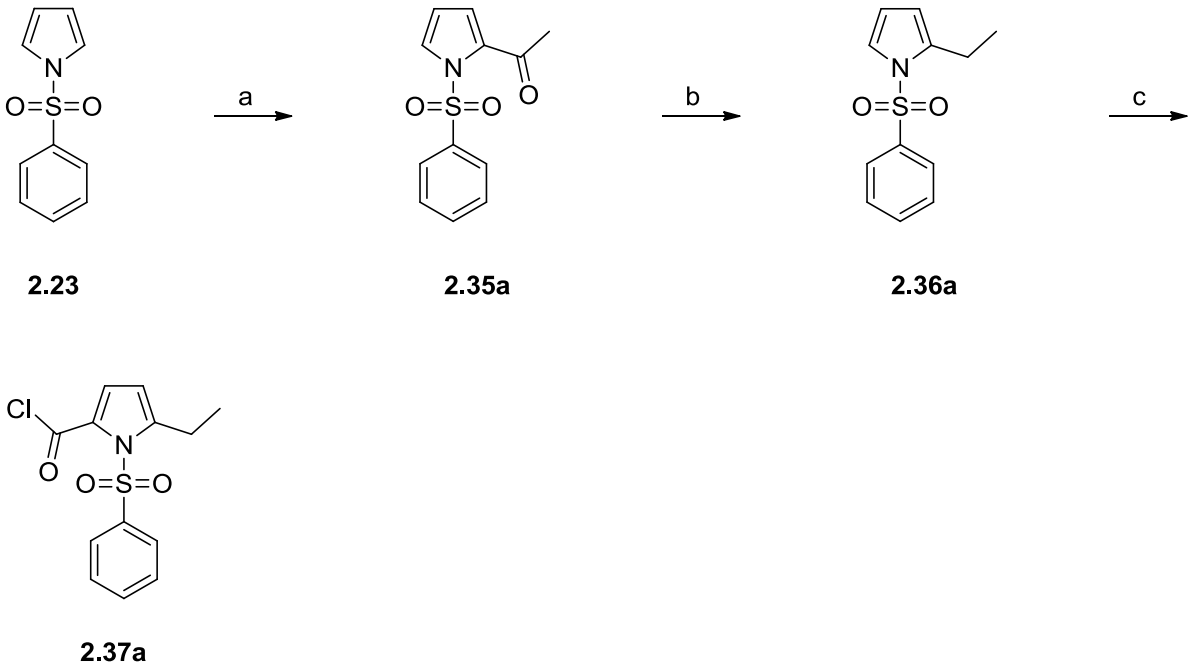
2.33 **2.34**

Reagent and Conditions: (a) LiI, pyridine, reflux.

Scheme 2.15: Formation of Substituted Diels-Alder Products

2.3.1. Synthesis of Ethyl Substituted Coupling Precursor 2.37a

The ethyl substituted precursor was selected to test the repeatability of this cyclisation. The construction of desired material **2.37a** is detailed below in **Scheme 2.16**.



Reagent and Conditions: (a) $BF_3{\cdot}OEt_2$, acetic anhydride, DCE, rt, 16h, 87%; (b) $AlCl_3$, *t*-$BuNH_2{\cdot}BH_3$, CH_2Cl_2, rt, 16h, 90%; (c) $AlCl_3$, $(COCl)_2$, DCE, 0 °C to rt, 6h, 95%.

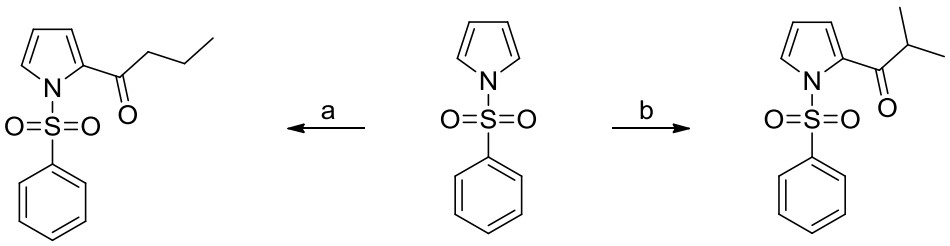
Scheme 2.16: Formation of the Acyl Chloride **2.37a**

The commercially available phenylsulfonyl pyrrole **2.23** was converted to 1-(1-phenylsulfonyl-*1H*-pyrrol-2-yl) ethanone **2.35a**.[151] In this reaction, acetic anhydride was added to a stirring suspension of $BF_3{\cdot}OEt_2$ in DCE at room temperature. After 15 minutes a solution of phenylsulfonyl pyrrole **2.23** in DCE was added. After stirring for 16 hours column chromatography afforded a bright-yellow solid (87%). The newly formed ketone **2.35a** was reduced using *t*-$BuNH_2{\cdot}BH_3$ in the presence of $AlCl_3$ at room temperature (90%).[152] The acyl chloride **2.37a** was formed as before by using $AlCl_3$ and oxalyl chloride (95%).[149]

2.3.2. Synthesis of Coupling Precursors 2.37b-c

The optimised route to acyl chloride **2.37a** was then applied to the synthesis of alternative coupling precursor analogues. The isobutyl and butyl substituted precursors were selected to test the repeatability of this cyclisation.

The synthesis commenced with the construction of desired materials **2.35b-c** as detailed below in **Scheme 2.17**.

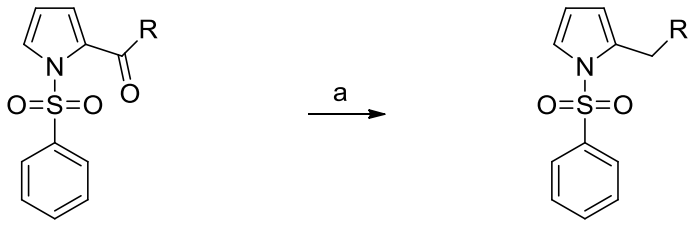


2.35b **2.23** **2.35c**

Reagent and Conditions: (a) Butyric anhydride, $BF_3 \cdot OEt_2$, DCE, rt, 16h, 80%; (b) *iso*-Butyric anhydride, $BF_3 \cdot OEt_2$, DCE, rt, 16h, 81%.

Scheme 2.17: Synthesis of Aryl Ketones **2.35b-c**

Yields for all the analogues were very satisfactory. Subsequently, *t*-$BuNH_2 \cdot BH_3$-$AlCl_3$ in dichloromethane was used to reduce arylalkyl ketones **2.35b-c** to the corresponding hydrocarbons ($ArCH_2R$) **2.36b-c**.



2.35b-c **2.36b-c**

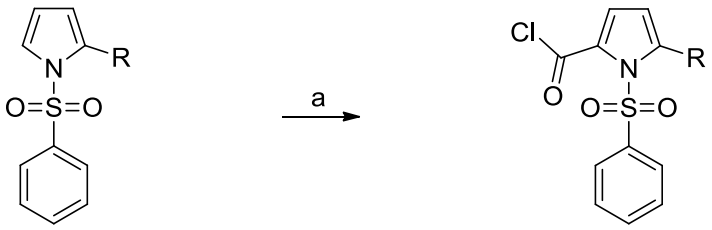
Reagent and Conditions: (a) $AlCl_3$, *t*-$BuNH_2 \cdot BH_3$, CH_2Cl_2, rt, 16h, yields, see **Table 2.2**.

Scheme 2.18: Reduction of Various Ketone Analogues

Entry	R	Compound reference	Yield (%)
1	Butyl	**2.36b**	86
2	*iso*-Butyl	**2.36c**	88

Table 2.2: Reduction of Ketone Analogues **2.35b-c**

The acyl chlorides **2.37b-c** were formed as before by using $AlCl_3$ and oxalyl chloride. The results are presented in **Table 2.3**.



2.36b-c **2.37b-c**

Reagent and Conditions: (a) $AlCl_3$, $(COCl)_2$, DCE, 0 °C to rt, 6h, yields, see **Table 2.3**.

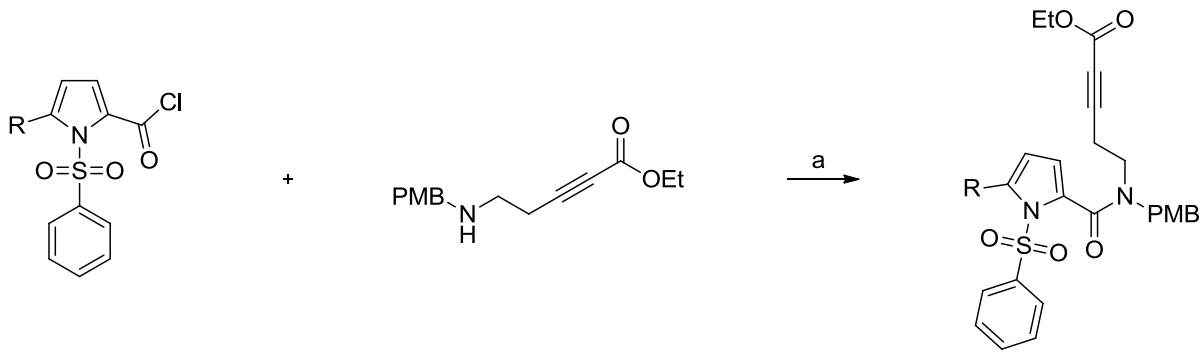
Scheme 2.19: Acylation of Various Aryl Analogues

Entry	R	Compound reference	Yield (%)
1	Butyl	**2.37b**	91
2	*iso*-Butyl	**2.37c**	86

Table 2.3: Acylation of Aryl Analogues **2.36b-c**

2.3.3. Synthesis of Cyclisation Precursors 2.38a-c

Yields for all three steps and for all the analogues were very satisfactory. The next step was to couple previously synthesised amine fragment **2.25** to the required acyl chlorides **2.37a-c**. The results are presented in **Table 2.4**.



2.37a-c **2.25** **2.38a-c**

Reagent and Conditions: (a) Et_3N, CH_2Cl_2, 0 °C to rt, 16h, yields, see **Table 2.4**.

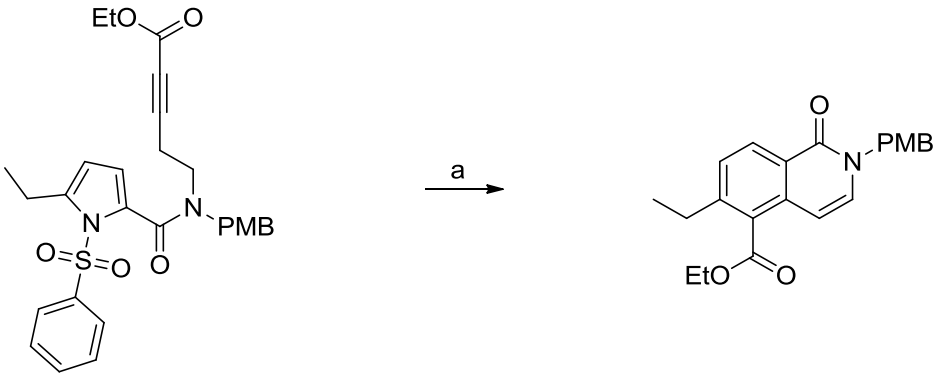
Scheme 2.20: Amide Coupling of Different Analogues

Entry	R	Compound reference	Yield (%)
1	Ethyl	**2.38a**	88%
2	Butyl	**2.38b**	87%
3	*iso*-Butyl	**2.38c**	90%

Table 2.4: Amide Coupling of Different Analogues

2.3.4. Thermal Cyclisations

The next step in the synthetic sequence was the thermal cyclisation reaction of the newly formed amide analogues **2.38a-c**. Compound **2.38a** was chosen as a test substrate for the cyclisation model. The newly formed cyclisation precursor **2.38a** was heated in anhydrous pyridine in the presence of LiI, resulting in the clean cyclisation of **2.38a** to form the isoquinolin-1(*2H*)-one derivative **2.39a** in moderate yield (56%). NMR and mass analysis of the product obtained revealed its structure to be isoquinolin-1(*2H*)-one derivative **2.39a** (**Scheme 2.21**).

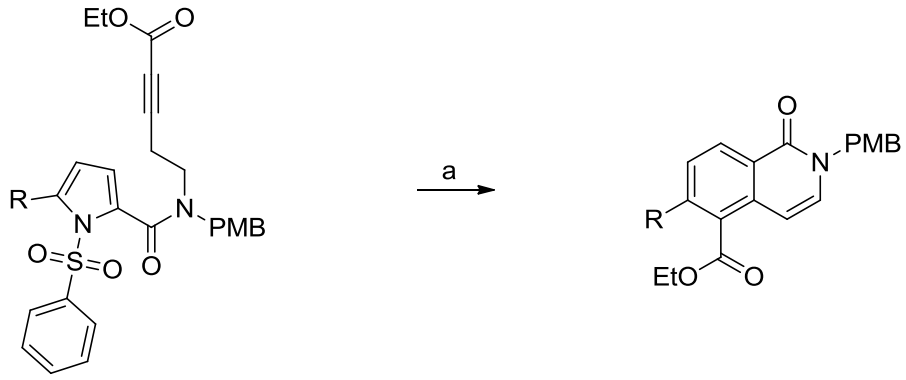


2.38a **2.39a**

Reagent and Conditions: (a) LiI, pyridine, reflux, 16h, 56%.

Scheme 2.21: Synthesis of Isoquinolin-1(*2H*)-one Derivative **2.39a**

The other two cyclisation precursor analogues **2.38b-c** were also subjected to cyclisation conditions and the results are shown below in **Table 2.5**.



2.38b-c **2.39b-c**

Reagent and conditions: (a) LiI, pyridine, reflux, 16h, yields, see **Table 2.5**.

Scheme 2.22: Thermal Cyclisation of Various Analogues

Entry	R	Compound reference	Yield (%)
1	Butyl	**2.39b**	51
2	*iso*-Butyl	**2.39c**	54

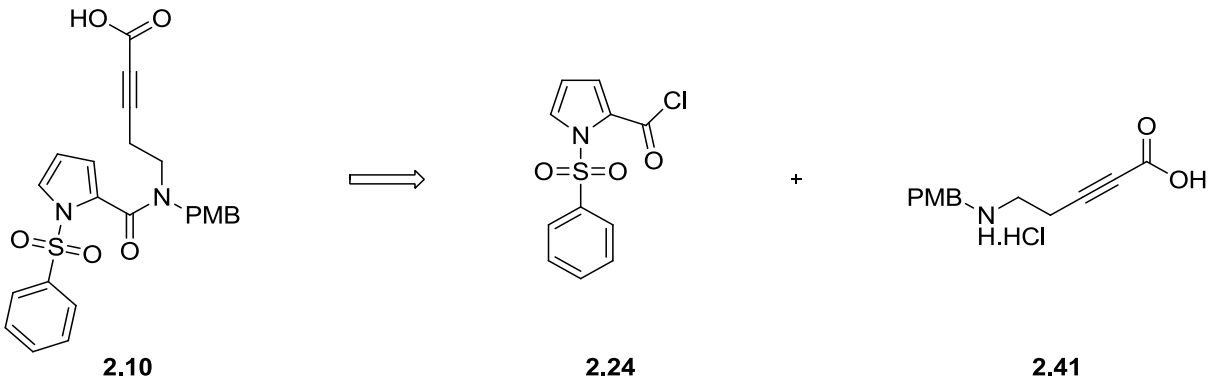
Table 2.5: Thermal Cyclisation of Precursors **2.38b-c**

This method for the synthesis of isoquinolin-1(*2H*)-one derivatives has proven highly effective. Furthermore, it can be utilised in studies towards the total synthesis of a number of biologically active natural products (for example see **Chapter 3**).

2.4. New Route for Synthesis of Carboxylic Acid 2.10

2.4.1. Outline of Investigation

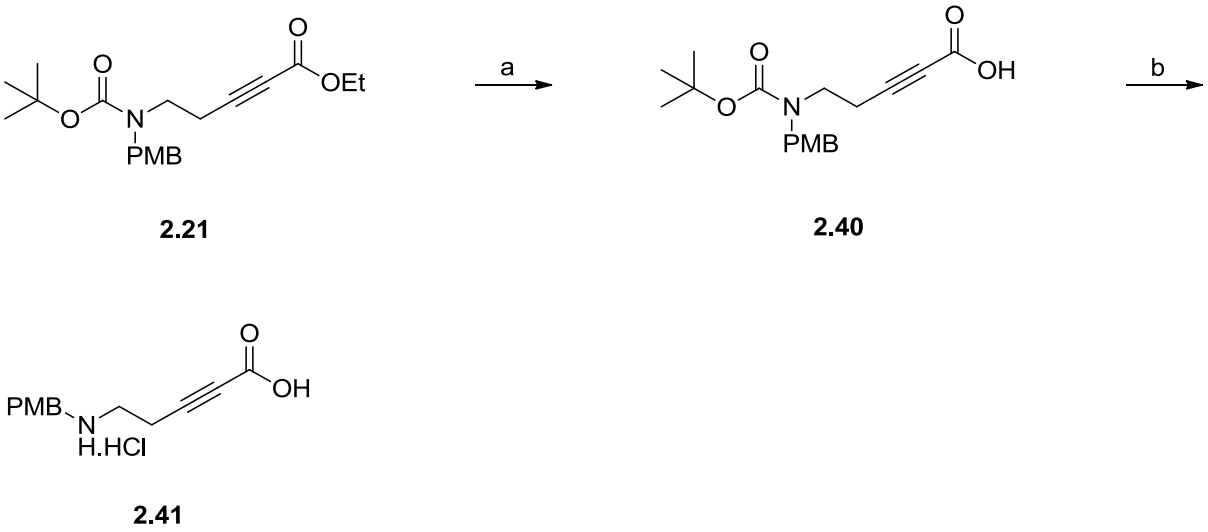
Having failed to find suitable conditions for the synthesis of carboxylic acid **2.10,** our attention was directed to finding an alternative route. Instead, it was suggested that the required carboxylic acid **2.10** could be formed by initially coupling the acyl chloride **2.24** with amine **2.41**, as shown in **Scheme 2.23**. The carboxylic acid moiety in compound **2.10** could then react with guanidine to form the desired compound **2.9**.



Scheme 2.23: Formation of Coupling Precursor **2.10**

2.4.2. Synthesis of Carboxylic Acid 2.10

Scheme 2.24 below illustrates the synthesis of desired amine **2.41**.

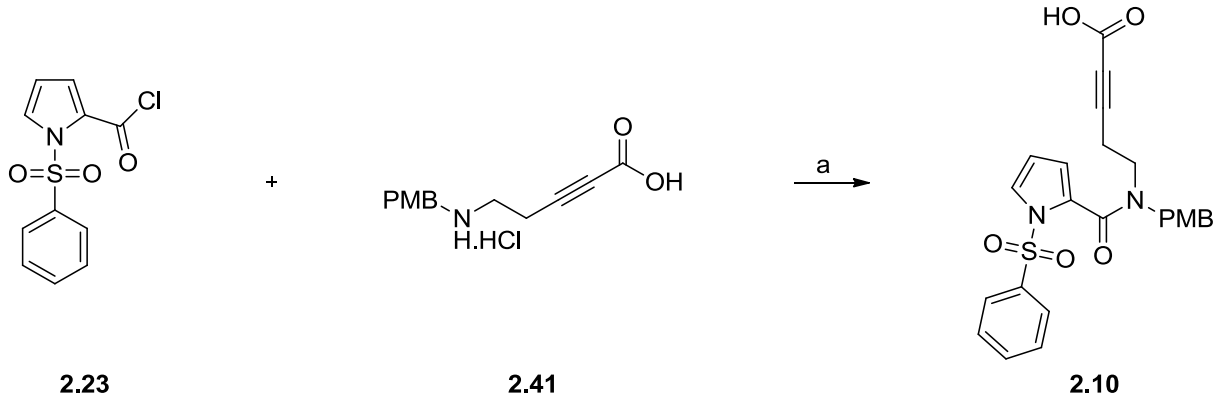


Reagents and Conditions: (a) KOH, MeOH, 0 °C to rt, 48h, 62%; (b) 4M HCl in dioxane, CH_2Cl_2, 0 °C to rt, 85%.

Scheme 2.24: Synthesis of Amine **2.41**

The saponification reaction was attempted with KOH in methanol and the required acid **2.40** was isolated in 62% yield. The Boc group was cleanly removed from the compound **2.40** with a solution of hydrogen chloride in dioxane. The amine salt of the compound formed was used without further purification for the subsequent coupling reaction. Once amine **2.41** was in hand, formation of carboxylic acid **2.10** could then be attempted through an amide

coupling reaction. Reaction of amine **2.41** with the acyl chloride **2.24** derived from 1-(phenylsulfonyl)-*1H*-pyrrole **2.23** in the presence of Et_3N as a base, yielded desired carboxylic acid **2.10**. This result corresponds with Dr. Nicola Chessum's previous work.[144]



2.23 **2.41** **2.10**

Reagent and Conditions: (a) Et_3N, CH_2Cl_2, 0 °C to rt, 16h, 44%.

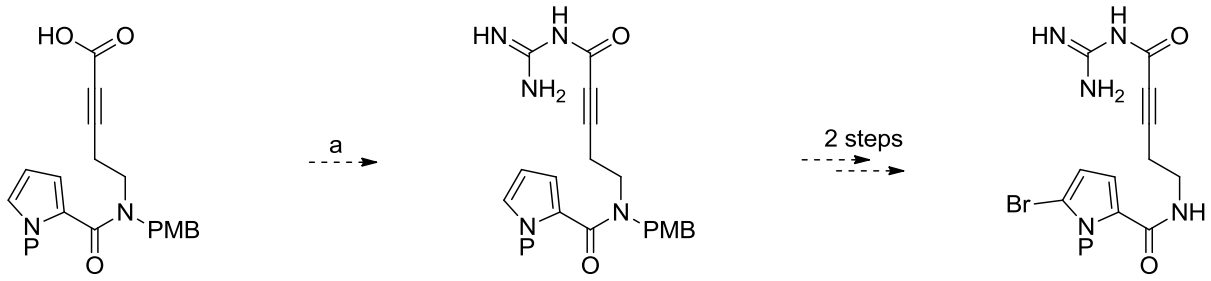
Scheme 2.25: Amide Coupling

The development of a route for the synthesis of carboxylic acid **2.10** has been developed and its syntheses successfully achieved. Once carboxylic acid **2.10** is in hand, the standard coupling conditions should provide the desired product **2.9**.

Chapter 3.

Conclusion & Future Work

This DPhil project has developed a robust route to an advanced intermediate in the synthesis of hymenialdisine **2.1**. Following the coupling reaction, two steps remain to achieve formation of the required cyclisation precursor **2.2** for the key tandem cyclisation as outlined in **Scheme 3.1**. The radical cascade reaction should afford the hymenialdisine **2.1** as initially proposed in **Scheme 2.2**. In addition, once compound **2.9** is obtained the utility of the radical tandem cyclisation can be tested.

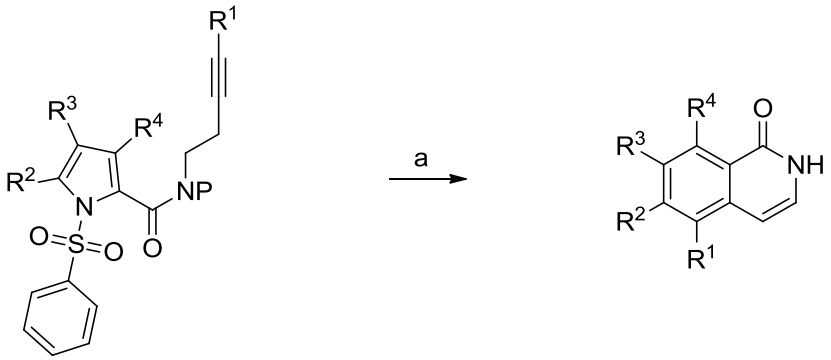


2.10 **2.9** **2.2**

Reagent and Conditions: (a) CDI, DMF, guanidine carbonate.

Scheme 3.1: Formation of Cyclisation Precursor **2.2**

The overall findings from this DPhil project will enable the rapid construction of complex ring systems as templates for drug design. This evidence gives support to the theory that a range of structures, richly substituted with functional groups can be synthesised using the thermal cyclisation reaction developed within the Parsons' research group.

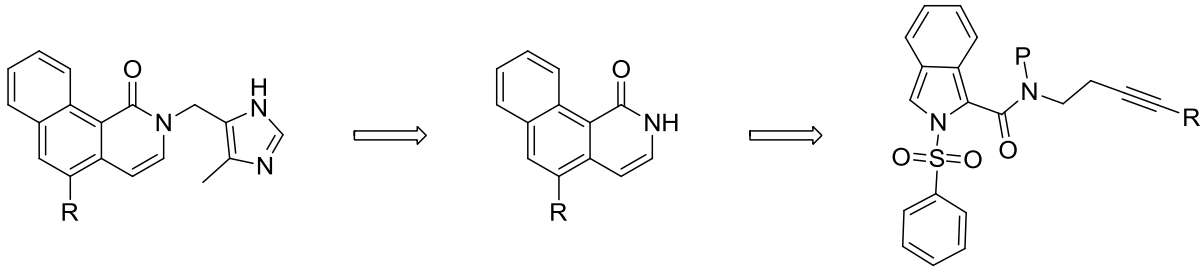


3.1 **3.2**

Reagent and conditions: (a) LiI, pyridine, reflux.

Scheme 2.15: Formation of Substituted Diels-Alder Products

For example, Matsui *et al.*[153] described the pharmacological evaluation of a series of isoquinolin-1(*2H*)-one derivatives which can be readily synthesized using the thermal cyclisation reaction developed.



3.5a-c **3.4a-c** **3.3a-c**

3.5a R=H, **3.5b** R=CH_2OH, **3.5c** R=$CONMe_2$

Scheme 3.2: Retrosynthetic Analysis of a Series of Isoquinolin-1(*2H*)-ones

We have reported the development of an efficient method for the *in-situ* conversion of conjugated alkynyl esters to conjugated allenyl esters, through the use of pyridine/LiI. The allenes have been previously obtained from elimination reactions of vinly halides in the presence of strong bases such as LDA and LiHMDS. These strong bases could pose a problem in terms of functional group tolerance in the synthesis of functionalized allenes.

Given the high synthetic potential of donor/acceptor-substituted allenes in organic synthesis,[154] it would be interesting to investigate the elimination pathway of *β*-iodovinyl esters.

Chapter 4.
Experimental
Section

4.1. General Procedure

Reactions were carried out under a nitrogen atmosphere in oven–dried glassware at room temperature (rt) unless otherwise stated. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Flash column chromatography was carried out on Merck Kieselgel (230-400 mesh). All reactions were followed by thin-layer chromatography (TLC) where possible; using Merck aluminium backed sheets coated with Merck Kieselgel 60 F254 (230-400 mesh) fluorescent treated silica. These were visualised under UV light (λmax= 254 or 365 nm) and developed using potassium permanganate or vanillin stains.

Reaction solvents were purified and dried according to literature methods; tetrahydrofuran and diethyl ether were distilled from sodium with benzophenone as an indicator. CH_2Cl_2, toluene, methanol and acetonitrile were distilled from CaH_2 under a positive pressure of dry nitrogen. Et_3N and pyridine were also distilled from CaH_2 and stored over KOH under nitrogen. Petroleum ether refers to the fraction boiling at 40-60 °C. Bulk solutions were evaporated under reduced pressure using a rotary evaporator. Other solvents and reagents were used as supplied. Brine refers to a saturated aqueous solution of NaCl. Salicylaldehyde phenylhydrazone was used as an indicator for the titration of organometallic species, including Grignard reagents.

^{1}H NMR spectra were recorded on a Varian 500 MHz machine (operating at ambient probe temperature using an internal deuterium lock). Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: δ/ppm (multiplicity, coupling constant J/Hz (where appropriate), number of protons). Multiplicity is abbreviated as follows: s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, app br d = apparent broad doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplet, q = quartet, dq = doublet of quartet, quint = quintet, m = multiplet, app s = apparent singlet, app d = apparent doublet, app t = apparent triplet, app q = apparent quartet. ^{13}C NMR spectra were recorded at 126 MHz. The ^{13}C NMR spectra are reported in δ/ppm. Two-dimensional (COSY, HSQC, H2BC, HMBC) NMR spectroscopy were used to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra.

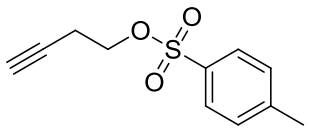
ESI Mass spectra were recorded on a Bruker Daltonics Apex III spectrometer with methanol or diethyl ether as solvents. EI mass spectra were recorded on a Fisons VG Autospec spectrometer by the internal service at the Department of Chemistry, University of Sussex.

IR spectra were recorded neat on a Perkin Elmer Spectrum One FT-IR spectrometer with a diamond ATR module and only selected maximum absorbances (νmax) of the most intense peaks are reported (cm^{-1}).

Melting points were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celsius (°C).

4.2. Compounds

But-3-yn-1-yl 4-methylbenzenesulfonate: (2.18)



$C_{11}H_{12}O_3S$

To a stirred solution of 3-butyn-1-ol **2.17** (10.0 g, 10.80 mL, 142.67 mmol) and pyridine (22.57 g, 22.97 mL, 285.34 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C was added *para*-toluenesulfonyl chloride (40.8 g, 214.00 mmol). The reaction was allowed to warm to rt and left to stir for 16 hours. Subsequently, the reaction mixture was concentrated *in vacuo* and the resultant residue partitioned between diethyl ether and water. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic layers were combined, washed once with 1.0M aqueous HCl solution, washed once with saturated aqueous $NaHCO_3$ solution, washed once with water and washed once with brine. The solution was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.18** was purified by flash chromatography on a silica gel column eluting with 40% ethyl acetate in petroleum ether to give the title compound **2.18** (31.09 g, 97%) as a yellow oil.
Spectroscopic data are in agreement with the literature values.[155]

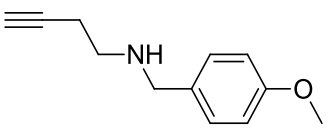
IR (neat) ν (cm^{-1}) 3294, 2963, 2928, 2156, 1323, 1175, 981, 905, 637.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 4.04 (t, J = 6.9 Hz, 2H), 2.49 (td, J = 6.9, 2.6 Hz, 2H), 2.38 (s, 3H), 1.95 (t, J = 2.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0 (C), 132.7 (C), 129.9 (CH), 127.8 (CH), 78.5 (C), 70.8 (CH), 67.5 (CH_2), 21.5 (CH_3), 19.3 (CH_2).

HMRS (ESI) calculated for $C_{11}H_{13}O_3S$ $[M+H]^+$ 225.0585, found 225.0583.

_N_-(4-Methoxybenzyl)but-3-yn-1-amine: (2.19)



$C_{12}H_{15}NO$

To a stirred solution of 4-methoxybenzylamine (34.07 g, 32.44 mL, 248.34 mmol) and tosylate **2.18** (27.85 g, 124.17 mmol) in anhydrous DMSO (300 mL) was added sodium iodide (0.69 g, 4.59 mmol). The reaction was left to stir at rt for 16 hours, subsequently the reaction mixture was poured into 2% aqueous NaOH solution. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.19** was purified by flash chromatography on a silica gel column eluting with 100% diethyl ether to give the title compound **2.19** (19.51 g, 83%) as a pale yellow oil.
Spectroscopic data are in agreement with the literature values.[156]

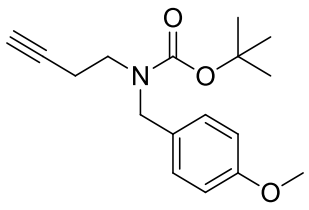
IR (neat) *v* (cm^{-1}) 3292, 3061, 3031, 2952, 2916, 2835, 2116, 1611, 1585, 1512, 1462, 1300, 1246, 1176, 1109, 1035, 815, 638.

^{1}H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 3.74 (s, 2H), 2.78 (t, *J* = 6.6 Hz, 2H), 2.39 (dt, *J* = 6.6, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.62 (br s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6 (C), 132.5 (C), 129.5 (CH), 114.1 (CH), 82.9 (C), 70.0 (CH), 55.5 (CH_3), 53.1 (CH_2), 47.5 (CH_2), 19.9 (CH_2).

HMRS (ESI) calculated for $C_{12}H_{15}NONa$ $[M+Na]^+$ 212.1046, found 212.1046.

tert-Butyl but-3-yn-1-yl(4-methoxybenzyl)carbamate: (2.20)



$C_{17}H_{23}NO_3$

To a stirred solution of *N*-(4-methoxybenzyl)but-3-yn-1-amine **2.19** (16.58 g, 87.6 mmol) and pyridine (8.67 g, 8.82 mL, 109.5 mmol) in dry diethyl ether (200 mL) at 0 °C was added di-*tert*-butyl dicarbonate (23.9 g, 25.19 mL, 109.5 mmol). The resultant solution was allowed to warm to rt and left to stir for 16 hours. Subsequently, the reaction mixture was quenched with water. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.20** was purified by flash chromatography on a silica gel column eluting with 10% ethyl acetate in petroleum ether to give the title compound **2.20** (24.59 g, 97%) as a pale yellow oil.
Spectroscopic data are in agreement with the literature values.[156]

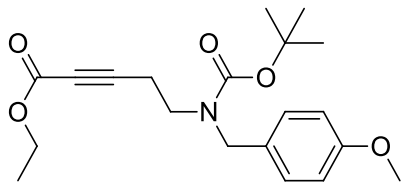
IR (neat) ν (cm^{-1}) 3294, 3064, 3002, 2975, 2934, 2836, 2119, 1692, 1612, 1513, 1465, 1411, 1366, 1248, 1166, 1121, 1036, 882, 774, 638.

^{1}H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 7.16 (br s, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.43 (s, 2H), 3.77 (s, 3H), 3.31 (br d, *J* = 36.3 Hz, 2H), 2.35 (br d, *J* = 27.1 Hz, 2H), 1.94 (t, *J* = 2.3 Hz, 1H), 1.47 (br s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 159.2 (C), 155.7 (C), 130.6 (C), 129.4 (CH), 114.5 (CH), 82.1 (C), 80.0 (C), 70.1 (CH), 55.4 (CH_3), 50.9 (CH_2), 45.6 (CH_2), 28.7 (CH_3), 18.6 (CH_2); *Rotamer B*; 155.6 (C), 128.9 (CH), 82.2 (C), 50.0 (CH_2), 45.9 (CH_2), 18.3 (CH_2).

HMRS (ESI) calculated for $C_{17}H_{23}NO_3Na$ $[M+Na]^+$ 312.1570, found 312.1547.

Ethyl 5-((*tert*-butoxycarbonyl)(4-methoxybenzyl)amino)pent-2-ynoate: (2.21)



$C_{20}H_{27}NO_5$

To a stirred solution of alkyne **2.20** (21.10 g, 72.92 mmol) in dry THF (200 mL) at -78 ºC was added *n*-BuLi (2.3 M solution in hexanes, 33.29 mL, 76.56 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of ethyl chloroformate (11.87 g, 10.41 mL, 109.38 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched at 0 °C with a saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, then brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow liquid. The crude product **2.21** was purified by flash chromatography on a silica gel column eluting with 30% ethyl acetate in petroleum ether to give the title compound **2.21** (25.18 g, 91%) as a pale yellow oil.

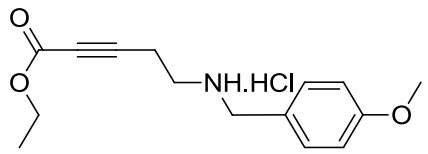
IR (neat) *v* (cm^{-1}) 3063, 2977, 2935, 2837, 2237, 1704, 1612, 1513, 1468, 1408, 1366, 1282, 1250, 1164, 1072, 1036, 887, 845, 755.

^1H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 7.13 (br s, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 4.40 (s, 2H), 4.15 (app. dd, *J* = 13.6, 6.7 Hz, 2H), 3.74 (s, 3H), 3.33 (br d, *J* = 21.0 Hz, 2H), 2.46 (br d, *J* = 35.5 Hz, 2H), 1.45 (s, 9H), 1.24 (t, *J* =7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 159.3 (C), 155.7 (C), 153.8 (C), 130.3 (C), 129.4 (CH), 114.3 (CH), 86.5 (C), 80.3 (C), 74.7 (C), 62.1 (CH_2), 55.6 (CH_3), 50.1 (CH_2), 44.7 (CH_2), 28.6 (CH_3), 18.6 (CH_2), 14.5 (CH_3); *Rotamer B*; 155.6 (C), 129.0 (CH), 114.0 (CH), 87.0 (C), 80.2 (C), 60.6 (CH_2), 51.1 (CH_2), 45.0 (CH_2), 28.4 (CH_3), 18.6 (CH_2), 14.3 (CH_3).

HMRS (ESI) calculated for $C_{20}H_{27}NO_5Na$ $[M+Na]^+$ 384.1781, found 384.1783.

Ethyl 5-((4-methoxybenzyl)amino)pent-2-ynoate hydrochloride: (2.22)



$C_{15}H_{20}ClNO_3$

To a stirred solution of carbamate **2.21** (22.0 g, 60.87 mmol) in dry CH_2Cl_2 (80 mL) at 0 °C was added a 4M solution of HCl in dioxane (182.6 mL, 730.0 mmol). The reaction was allowed to warm to rt and left to stir for 4 hours, during which time the formation of white precipitates were observed. The solvent was removed *in vacuo* to afford a pale brown solid. This solid was triturated with diethyl ether to afford a white solid which was collected by filtration and washed well with diethyl ether, after drying under high vacuum the title product obtained was a white solid. The crude product **2.22** was used directly in the next step without further purification (17.22 g, 95%).

m.p.: 148 - 149 °C

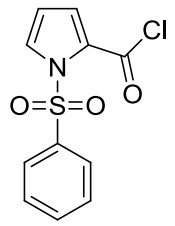
IR (neat) ν (cm^{-1}) 2978, 2923, 2854, 2237, 1703, 1612, 1586, 1517, 1457, 1261, 1161, 1074, 1035, 884, 754.

^{1}H NMR (500 MHz, DMSO-d_6, broadened signals were observed) δ 9.57 (br s, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.06 (s, 2H), 3.76 (s, 3H), 3.08 (t, *J* = 7.4 Hz, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 160.1 (C), 153.0 (C), 132.0 (C), 124.0 (CH), 114.4 (CH), 85.2 (C), 74.7 (C), 62.3 (CH_2), 55.6 (CH_3), 49.7 (CH_2), 43.9 (CH_2), 15.8 (CH_2), 14.23 (CH_3).

HMRS (ESI) calculated for $C_{15}H_{19}NO_3Na$ $[M\text{-}HCl+Na]^+$ 284.1257, found 284.1285.

1-(Phenylsulfonyl)-*1H*-pyrrole-2-carbonyl chloride: (2.24)



$C_{11}H_8ClNO_3S$

To a stirred suspension of aluminium chloride (6.66 g, 50 mmol) in dry 1,2-dichloroethane (60 mL) at 0 °C was added oxalyl chloride (6.34 g, 4.30 mL, 50 mmol). The reaction was left to stir for 30 minutes at 0 °C before the addition of 1-phenylsulfonyl-*1H*-pyrrole **2.23** (2.07 g, 10 mmol) in dry 1,2-dichloroethane (15 mL). The resultant solution was allowed to warm to rt and left to stir for 2 hours. Subsequently, it was poured into a mixture of ice and water and the product was extracted twice with diethyl ether. The organic layers were combined, washed once with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a brown oil. The crude product **2.24** was used directly in the next step without future purifications (2.55 g, 95%).
Spectroscopic data are in agreement with the literature values.[157]

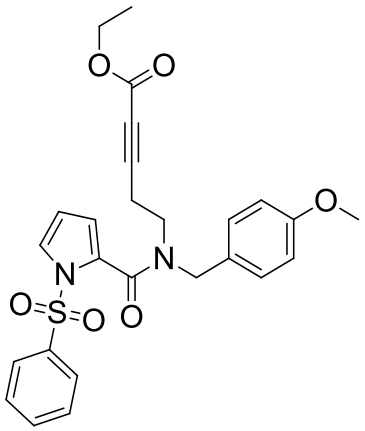
IR (neat) ν (cm^{-1}) 3140, 2923, 2854, 1756, 1446, 1423, 1372, 1188, 1170, 1027.

^{1}H NMR (300 MHz, $CDCl_3$, broadened signals were observed) δ 7.91 (br s, 1H), 7.82 (app. dd, *J* = 3.0, 2.0 Hz, 2H), 7.57 (app. tt, *J* = 7.5, 1.0 Hz, 1H), 7.48 (app. tt, J = 7.5, 1.0 Hz, 2H), 7.41 (app. dd, *J* = 4.0, 2.0 Hz, 1H), 6.35 (app. dd, *J* = 4.0, 3.0 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.1 (C), 137.8 (C), 135.0 (CH), 133.7 (CH), 132.4 (CH), 129.5 (CH), 128.7 (CH), 126.6 (C), 112.0 (CH).

m/z (EI^+) 269 (M^+, 11%), 234 (98), 141 (59), 93 (78), 77 (100), 51 (72).

Ethyl 5-(*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-*1H*-pyrrole-2-carboxamido)pent-2-ynoate: (2.8)



$C_{26}H_{26}N_2O_6S$

Initially, the free base of amine **2.25** was prepared by partitioning the salt between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The aqueous and organic layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined extracts were washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo.* The free base of amine **2.25** was then used in the next step.

To a stirred solution of free base of amine **2.25** (2.19 g, 8.15 mmol) and triethylamine (1.50 g, 2.07 mL, 14.82 mmol) in dry THF (30 mL) at 0 °C was added acid chloride **2.24** (2.0 g, 7.41 mmol) in dry THF (15 mL). The reaction was allowed to warm to rt and left to stir for 8 hours. The reaction was then quenched with cold water, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give an orange oil. The crude product **2.8** was purified by flash chromatography on a silica gel column eluting with 50% diethyl ether in hexanes to give the title compound **2.8** (3.29 g, 90%) as a pale yellow foam.

Spectroscopic data are in agreement with the literature values[144]

IR (neat) ν (cm^{-1}) 2923, 2855, 2239, 1706, 1643, 1455, 1365, 1255, 1236, 1150.

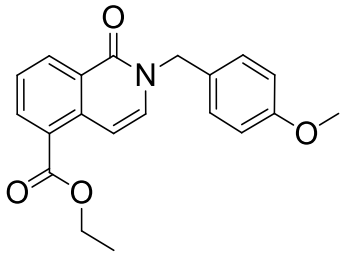
^{1}H NMR (500 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 7.90 (d, *J* = 7.0 Hz, 2H), 7.55 – 7.45 (m, 2H), 7.43 –7.38 (m, 1H), 7.15 (br s, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.25 (br s, 0.7H), 6.12 (br s, 0.7H), 4.45 (s, 1.4H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.71 (s, 3H), 3.49 (t, *J* = 6.5 Hz, 1.4H), 2.60 (t, *J* = 6.5 Hz, 1.4H), 1.19 (t, *J* = 7.0 Hz, 3H); *Rotamer B*; 6.30 (br s, 0.3H), 6.17 (br s, 0.3H), 4.68 (s, 0.6H), 3.40 – 3.30 (m, 0.6H), 2.45 – 2.35 (m, 0.6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.0 (C), 159.7 (C), 153.9 (C), 138.7 (C), 134.6 (CH), 129.5 (CH), 129.2 (CH), 128.4 (CH), 128.2 (C), 123.3 (CH), 114.7 (CH), 114.2 (CH), 112.5 (CH), 86.8 (C), 74.6 (C), 62.3 (CH_2), 55.6 (CH_3), 53.3 (CH_2), 43.0 (CH_2), 17.1 (CH_2), 14.4 (CH_3).

HMRS (ESI) calculated for $C_{26}H_{26}N_2O_6SNa$ $[M+Na]^+$ 517.1403, found 517.1393.

m/z (EI^+) 495 ($M+H^+$, 25%), 450 (75), 260 (41), 234 (73), 121 (100), 77 (76).

Ethyl 2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisoquinoline-5-carboxylate: (2.11)



$C_{20}H_{19}NO_4$

To a stirred solution of amide **2.8** (1.5 g, 3.03 mmol) in anhydrous pyridine (30 mL) was added lithium iodide (0.40 g, 3.03 mmol). The mixture was heated at reflux for 16 hours, cooled to rt and diluted with CH_2Cl_2. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with CH_2Cl_2. The organic layers were combined, washed once with saturated

aqueous $NaHCO_3$ solution, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow tinted solid. The crude product **2.11** was purified by flash chromatography on a silica gel column eluting with 50% diethyl ether in hexanes to give the title compound **2.11** (0.53 g, 52%) as white solid. Spectroscopic data are in agreement with the literature values[144]

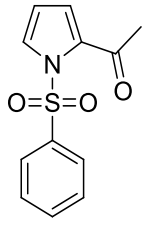
IR (neat) ν (cm^{-1}) 2926, 1708, 1651, 1621, 1591, 1513, 1254, 1126.

^1H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 5.06 (s, 2H), 4.32 (q, *J* = 7.0 Hz, 2H), 3.72 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4 (C), 161.7 (C), 159.3 (C), 136.6 (C), 135.1 (CH), 132.7 (CH), 132.6 (CH), 129.4 (CH), 128.5 (C), 127.3 (C), 125.7 (C), 125.6 (CH), 114.1 (CH), 103.9 (CH), 61.1 (CH_2), 55.1 (CH_3), 51.1 (CH_2), 14.1 (CH_3).

HMRS (ESI) calculated for $C_{20}H_{19}NO_4Na$ $[M+Na]^+$ 360.1212, found 360.1215.

1-(1-(Phenylsulfonyl)-*1H*-pyrrol-2-yl)ethanone: (2.35a)



$C_{12}H_{11}NO_3S$

To a stirred solution of acetic anhydride (2.17 g, 2.0 mL, 21.23 mmol) in dry 1,2-dichloroethane (60 mL) was added boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$; 5.48 g, 4.76

mL, 38.6 mmol). The reaction mixture was left to stir at rt for 10 minutes before the addition of 1-phenylsulfonyl-*1H*-pyrrole **2.23** (4.0 g, 19.30 mmol) in dry 1,2-dichloroethane (20 mL). The resultant solution was allowed to stir for a further 8 hours. Subsequently, it was poured into a mixture of ice and water and the product was extracted twice with diethyl ether. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a dark yellow liquid. The crude product **2.35a** was purified by flash chromatography on a silica gel column eluting with 20% ethyl acetate in petroleum ether to give the title compound **2.35a** (4.18 g, 87%) as a dark yellow solid.
Spectroscopic data are in agreement with the literature values.[158]

m.p.: 96.1 - 98.0 °C

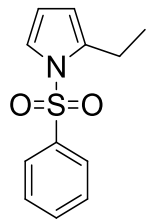
IR (neat) ν (cm^{-1}) 3165, 2972, 2925, 2854, 1676, 1583, 1436, 1358, 1322, 1180, 1142, 1060.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.83 (dd, *J* = 1.8, 3.2 Hz. 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H), 7.06 (dd, *J* = 1.8, 3.4 Hz, 1H), 6.35 (t, *J* = 3.4 Hz, 1H), 2.36 (br s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 185.7 (C), 138.9 (C), 133.6 (CH), 133.3 (C), 130.3 (CH), 128.6 (CH), 128.1 (CH), 124.3 (CH), 110.4 (CH), 26.9 (CH_3).

HMRS (ESI) calculated for $C_{12}H_{11}NO_3SNa$ $[M+Na]^+$ 272.0351, found 272.0350.

2-Ethyl-1-(phenylsulfonyl)-*1H*-pyrrole: (2.36a)



$C_{12}H_{13}NO_2S$

To a stirred suspension of aluminium chloride (6.17 g, 45.13 mmol) in CH_2Cl_2 (100 mL) was added borane *tert*-butylamine complex (*t*-$BuNH_2 \cdot BH_3$; 7.85 g, 90.26 mmol). The reaction was left to stir for 2 hours at rt before the addition of 1-(1-(phenylsulfonyl)-*1H*-pyrrol-2-yl)ethanone **2.35a** (3.75 g, 15.04 mmol) in CH_2Cl_2 (25 mL). The resultant solution was allowed to stir at rt for a further 16 hours. Subsequently, it was poured into a mixture of ice and water and the product was extracted twice with diethyl ether. The organic layers were combined, washed once with 3.0 M aqueous HCl solution, washed once with saturated aqueous $NaHCO_3$ solution, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a pale yellow solid. The crude product **2.36a** was purified by flash chromatography on a silica gel column eluting with 25% diethyl ether in petroleum ether to give the title compound **2.36a** (3.25 g, 92%) as a white solid. Spectroscopic data are in agreement with the literature values.[159]

m.p.: 57.0 - 58.0 °C

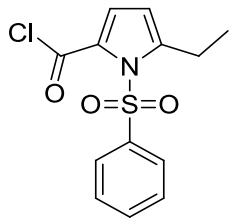
IR (neat) ν (cm^{-1}) 3140, 2924, 2855, 1605, 1447, 1390, 1361, 1169, 1043.

^{1}H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 7.75 (d, J = 8.2 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.32 (br s, 1H), 6.22 (t, J = 3.0 Hz, 1H), 6.01 (br s, 1H), 2.70 (q, J = 7.4 Hz, 2H), 1.16 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.4 (C), 137.3 (C), 133.6 (CH), 129.3 (CH), 126.6 (CH), 122.2 (CH), 111.4 (CH), 111.1 (CH), 20.5 (CH_2), 12.7 (CH_3).

HMRS (ESI) calculated for $C_{12}H_{13}NO_2SNa$ $[M+Na]^+$ 258.0565, found 258.0559.

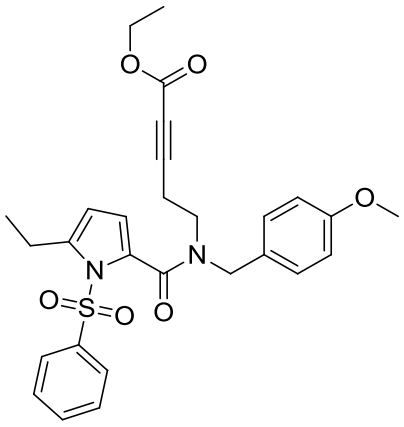
5-Ethyl-1-phenylsulfonyl-*1H*-pyrrole-2-carbonyl chloride: (2.37a)



$C_{15}H_{12}ClNO_3S$

To a stirred suspension of aluminium chloride (3.4 g, 25.50 mmol) in dry 1,2-dichloroethane (50 mL) at 0 °C was added oxalyl chloride (3.24 g, 2.19 mL, 25.50 mmol). The reaction was left to stir for 30 minutes at 0 °C before the addition of 2-Ethyl-1-(phenylsulfonyl)-*1H*-pyrrole **2.36a** (1.2 g, 5.10 mmol) in dry 1,2-dichloroethane (5 mL). The resultant solution was allowed to warm to rt and left to stir for 2 hours. Subsequently, it was poured into a mixture of ice and water and the product was extracted twice with diethyl ether. The organic layers were combined, washed once with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a brown oil (1.44 g, 95%). The crude product **2.37a** was used directly in the next reaction without further purification.

Ethyl 5-(5-ethyl-*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-*1H*-pyrrole-2-carboxamido)pent-2-ynoate: (2.38a)



$C_{28}H_{30}N_2O_6S$

To a stirred solution of free base of amine **2.25** (1.39 g, 5.32 mmol) and triethylamine (0.98 g, 1.35 mL, 9.68 mmol) in dry THF (25 mL) at 0 °C was added acid chloride **2.37a** (1.44 g, 4.84 mmol) in dry THF (15 mL). The reaction was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched with water, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give an pale orange oil. The crude product **2.38a** was purified by flash chromatography on a silica gel column eluting with 40% diethyl ether in hexanes to give the title compound **2.38a** (2.22 g, 88%) as a yellow foam.

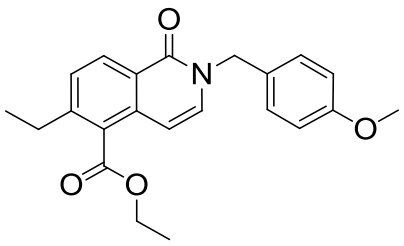
IR (neat) ν (cm^{-1}) 2936, 2235, 1705, 1634, 1512, 1448, 1365, 1245, 1174, 1071.

^{1}H NMR (500 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 8.16 (d, *J* = 7.7 Hz, 1.4H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 1.4H), 6.87 – 6.82 (m, 1.4H), 6.28 (d, *J* = 3.4 Hz, 0.7H), 5.92 (d, *J* = 3.4 Hz, 0.7H), 4.56 (s, 1.4H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 2.1H), 3.59 (br s, 1.4H), 2.69 (app. t, *J* = 6.9 Hz, 3.4H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.15 – 1.10 (m, 3H); *Rotamer B*; 8.19 (d, *J* = 7.7 Hz, 0.6H), 7.33 (d, *J* = 8.5 Hz, 0.6H), 6.87 – 6.82 (m, 0.6H), 6.32 (d, *J* = 3.4 Hz, 0.3H), 5.96 (d, *J* = 3.1 Hz, 0.3H), 4.76 (s, 0.6H), 3.73 (s, 0.9H), 3.50 (t, *J* = 7.0 Hz, 0.6H), 2.52 (t, *J* = 7.2 Hz, 0.6H).

^{13}C NMR (126 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 164.7 (C), 159.3 (C), 153.4 (C), 139.1 (C), 138.6 (C), 134.0 (CH), 129.3 (C), 129.2 (CH), 128.9 (CH), 127.9 (C), 127.7 (CH), 114.2 (CH), 112.3 (CH), 110.1 (CH), 86.6 (C), 74.1 (C), 61.7 (CH_2), 55.2 (CH_3), 52.8 (CH_2), 42.5 (CH_2), 20.8 (CH_2), 18.3 (CH_2), 13.9 (CH_3), 12.4 (CH_3); *Rotamer B*; 164.9 (C), 159.1 (C), 153.2 (C), 139.2 (C), 138.5 (C), 129.7 (CH), 128.4 (C), 127.6 (CH), 114.0 (CH), 112.7 (CH), 110.1 (CH), 85.3 (C), 74,7 (C), 61.8 (CH_2), 55.1 (CH_3), 47.4 (CH_2), 45.6 (CH_2), 16.4 (CH_2).

HMRS (ESI) calculated for $C_{28}H_{30}N_2O_6SNa$ $[M+Na]^+$ 545.1722, found 545.1720.

Ethyl 6-ethyl-2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisoquinoline-5-carboxylate: (2.39a)



$C_{22}H_{23}NO_4$

To a stirred solution of amide **2.38a** (1.5 g, 2.89 mmol) in anhydrous pyridine (30 mL) was added lithium iodide (0.38 g, 2.89 mmol). The mixture was heated at reflux for 8 hours, cooled to rt and diluted with CH_2Cl_2. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with CH_2Cl_2. The organic layers were combined, washed once with saturated aqueous $NaHCO_3$ solution, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow tinted solid. The crude product **2.39a** was purified by flash chromatography on a silica gel column eluting with 50% diethyl ether in hexanes to give the title compound **2.39a** (0.59 g, 56%) as a yellow amorphous solid.

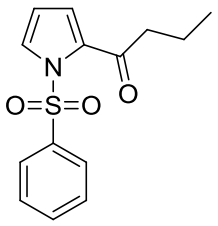
IR (neat) ν (cm^{-1}) 2954, 2921, 2856, 1721, 1651, 1625, 1587, 1510, 1458, 1325, 1298, 1245, 1128, 1021.

^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 7.7 Hz, 1H), 6.84 (d, J = 8.6 Hz, 2H), 6.47 (d, J = 7.6 Hz, 1H), 5.13 (s, 2H), 4.46 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 2.77 (q, J = 7.6 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H), 1.30 – 1.25 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6 (C), 161.6 (C), 159.3 (C), 146.1 (C), 134.2 (C), 132.1 (CH), 129.7 (CH), 129.4 (CH), 129.0 (C), 128.7 (C), 127.7 (CH), 124.6 (C), 114.2 (CH), 103.2 (CH), 61.5 (CH_2), 55.2 (CH_3), 51.1 (CH_2), 27.4 (CH_2), 15.4 (CH_3), 14.2 (CH_3).

HMRS (ESI) calculated for $C_{22}H_{23}NO_4Na$ $[M+Na]^+$ 388.1519, found 388.1520.

1-(1-(Phenylsulfonyl)-*1H*-pyrrol-2-yl)butan-1-one: (2.35b)



$C_{14}H_{15}NO_3S$

To a stirred solution of butyric anhydride (3.36 g, 3.47 mL, 21.23 mmol) in dry 1,2-dichloroethane (80 mL) was added boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$; 5.48 g, 4.76 mL, 38.6 mmol). The reaction was left to stir at rt for 10 minutes before the addition of 1-phenylsulfonyl-*1H*-pyrrole **2.23** (4.0 g, 19.30 mmol) in dry 1,2-dichloroethane (20 mL). The resultant solution was allowed to stir at rt for a further 8 hours. Subsequently, it was poured into a mixture of ice and water and the product was extracted twice with diethyl ether. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a dark brown liquid. The crude product **2.35b** was purified by flash chromatography on a silica gel column eluting with 15% ethyl acetate in petroleum ether to give the title compound **2.35b** (4.28 g, 80%) as a brown oil.

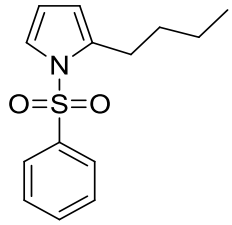
IR (neat) ν (cm^{-1}) 3152, 2967, 2875, 1674, 1596, 1467, 1440, 1365, 1172, 1143, 1090, 1063, 669.

^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.2 Hz, 2H), 7.82 (dd, J = 1.7, 3.2 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.06 (dd, J = 1.7, 3.2 Hz, 1H), 6.34 (t, J = 3.3 Hz, 1H), 2.58 (t, J = 7.4 Hz, 2H), 1.69 – 1.58 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.9 (C), 139.0 (C), 133.6 (CH), 133.5 (C), 130.0 (CH), 128.6 (CH), 128.0 (CH), 123.2 (CH), 110.3 (CH), 41.2 (CH_2), 18.3 (CH_2), 13.6 (CH_3).

HMRS (ESI) calculated for $C_{14}H_{15}NO_3SNa$ $[M+Na]^+$ 300.0675, found 300.0666.

2-Butyl-1-phenylsulfonyl-*1H*-pyrrole: (2.36b)



$C_{14}H_{17}NO_2S$

To a stirred suspension of aluminium chloride (5.48 g, 41.10 mmol) in dry CH_2Cl_2 (75 mL) was added borane *tert*-butylamine complex (*t*-$BuNH_2 \cdot BH_3$; 7.15 g, 82.21 mmol). The reaction mixture was left to stir at rt for 2 hours before the addition of 1-(1-(phenylsulfonyl)-*1H*-pyrrol-2-yl)butan-1-one **2.35b** (3.8 g, 13.70 mmol) in dry CH_2Cl_2 (25 mL). The resultant solution was allowed to stir at rt for a further 16 hours. Subsequently, it was poured into a mixture of ice and water and the product was extracted twice with diethyl ether. The organic layers were combined, washed once with 3.0 M aqueous HCl solution, washed once with saturated aqueous $NaHCO_3$ solution, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow solid. The crude product **2.36b** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in petroleum ether to give the title compound **2.36b** (3.21 g, 89%) as a yellow solid.

m.p.: 57.3 - 57.8 °C

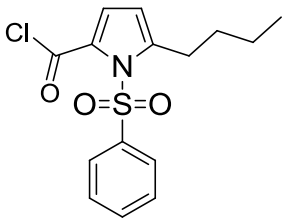
IR (neat) ν (cm^{-1}) 3153, 2932, 2853,1484, 1448, 1365, 1247, 1189, 1175, 1156, 1090, 668.

^{1}H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 7.75 (d, J = 8.0 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.30 (br s, 1H), 6.21 (t, J = 3.1 Hz, 1H), 6.00 (br s, 1H), 2.66 (t, J = 7.7 Hz, 2H), 1.56 – 1.49 (m, 2H), 1.37 – 1.29 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5 (C), 136.0 (C), 133.5 (CH), 129.2 (CH), 126.6 (CH), 122.2 (CH), 111.8 (CH), 111.3 (CH), 30.7 (CH_2), 26.8 (CH_2), 22.2 (CH_2), 13.7 (CH_3).

HMRS (ESI) calculated for $C_{14}H_{17}NO_2SNa$ $[M+Na]^+$ 286.0883, found 286.0873.

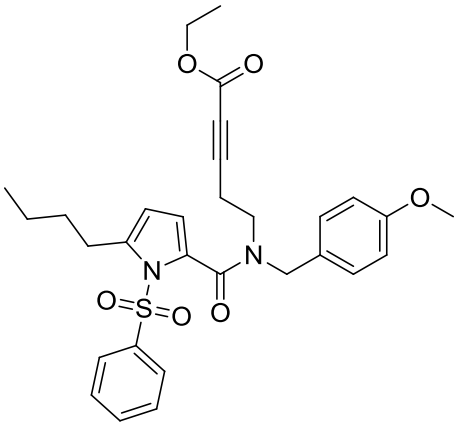
5-Butyl-1-phenylsulfonyl-*1H*-pyrrole-2-carbonyl chloride: (2.37b)



$C_{15}H_{16}ClNO_3S$

To a stirred suspension of aluminium chloride (3.04 g, 22.78 mmol) in dry 1,2-dichloroethane (50 mL) at 0 °C was added oxalyl chloride (2.89 g, 1.95 mL, 22.78 mmol). The reaction was left to stir for 30 minutes at 0 °C before the addition of 2-butyl-1-phenylsulfonyl-*1H*-pyrrole **2.36b** (1.2 g**,** 4.56 mmol) in dry 1,2-dichloroethane (15 mL). The resultant solution was allowed to warm to rt and left to stir for 2 hours. Subsequently, it was poured into a mixture of ice and water and the product was extracted twice with diethyl ether. The organic layers were combined, washed once with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a brown oil (1.38 g, 93%). The crude product **2.37b** was used directly in the next step without further purification.

Ethyl 5-(5-butyl-*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-*1H*-pyrrole-2-carboxamido)pent-2-ynoate: (2.38b)



$C_{30}H_{34}N_2O_6S$

To a stirred solution of free base of amine **2.25** (1.22 g, 4.67 mmol) and triethylamine (0.86 g, 1.18 mL, 8.50 mmol) in dry THF (20 mL) at 0 °C was added acid chloride **2.37b** (1.38 g, 4.25 mmol) in dry THF (10 mL). The reaction was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched with water, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give an orange oil. The crude product **2.38b** was purified by flash chromatography on a silica gel column eluting with 40% diethyl ether in hexanes to give the title compound **2.38b** (2.04 g, 87%) as a pale yellow foam.

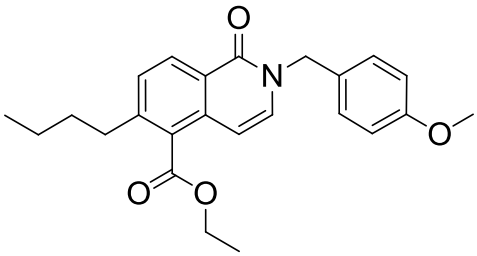
IR (neat) *v* (cm^{-1}) 2955, 2927, 2856, 1721, 1650, 1624, 1586, 1510, 1456, 1368, 1384, 1324, 1297, 1245, 1170, 1128, 1104, 1022, 926, 839, 810, 775, 723.

^{1}H NMR (500 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 8.18 (d, *J* = 7.9 Hz, 1.4H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 1.4H), 6.87 – 6.82 (m, 1.4H), 6.29 (d, *J* = 3.4 Hz, 0.7H), 5.93 (d, *J* = 3.4 Hz, 0.7H), 4.58 (s, 1.4H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.80 (s, 2.1H), 3.60 (br s, 1.4H), 2.71 (app. t, *J* = 7.2 Hz, 3.4H), 1.53 – 1.44 (m, 2H), 1.34 – 1.21 (m, 5H), 0.85 (t, *J* = 7.2 Hz, 3H); *Rotamer B*; 8.21 (d, *J* = 7.8 Hz, 0.6H), 7.35 (d, *J* = 8.4 Hz, 0.6H), 6.87 – 6.82 (m, 0.6H), 6.32 (d, *J* = 3.3 Hz, 0.3H), 5.98 (d, *J* = 3.0 Hz, 0.3H), 4.76 (s, 0.6H), 3.79 (s, 0.9H), 3.52 (t, *J* = 7.0 Hz, 0.6H), 2.54 (t, *J* = 7.0 Hz, 0.6H).

^{13}C NMR (126 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 164.7 (C), 159.3 (C), 153.4 (C), 138.7 (C), 137.8 (C), 133.9 (CH), 129.4 (C), 129.2 (CH), 128.9 (CH), 128.0 (C), 127.7 (CH), 114.2 (CH), 112.4 (CH), 110.7 (CH), 86.6 (C), 74.1 (C), 61.6 (CH_2), 55.1 (CH_3), 52.8 (CH_2), 42.5 (CH_2), 30.5 (CH_2), 27.1 (CH_2), 22.2 (CH_2), 16.3 (CH_2), 13.9 (CH_3), 13.7 (CH_3); *Rotamer B*; 164.9 (C), 159.1 (C), 153.2 (C), 138.6 (C), 138.0 (C), 129.7 (CH), 128.4 (C), 127.8 (CH), 114.0 (CH), 112.8 (CH), 110.9 (CH), 85.3 (C), 74.7 (C), 61.8 (CH_2), 55.1 (CH_3), 47.4 (CH_2), 45.6 (CH_2), 29.6 (CH_2), 27.1 (CH_2).

HMRS (ESI) calculated for $C_{30}H_{34}N_2O_6SNa$ $[M+Na]^+$ 573.2029, found 573.2047.

Ethyl 6-butyl-2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisoquinoline-5-carboxylate: (2.39b)



$C_{24}H_{27}NO_4$

To a stirred solution of amide **2.35b** (1.5 g, 2.72 mmol) in anhydrous pyridine (30 mL) was added lithium iodide (0.36 g, 2.72 mmol). The mixture was heated at reflux for 8 hours, cooled to rt and diluted with CH_2Cl_2. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with CH_2Cl_2. The organic layers were combined, washed once with saturated aqueous $NaHCO_3$ solution, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow solid. The crude product **2.36b** was purified by flash chromatography on a silica gel column eluting with 50% diethyl ether in hexanes to give the title compound **2.36b** (0.54 g, 51%) as a yellow oil.

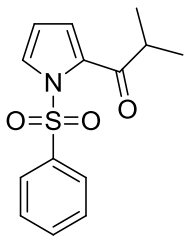
IR (neat) ν (cm^{-1}) 2954, 2921, 2865, 1721, 1651, 1625, 1586, 1510, 1455, 1300, 1245, 1128, 1022.

^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 7.7 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 6.48 (d, J = 7.7 Hz, 1H), 5.12 (s, 2H), 4.45 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 2.74 (t, J = 7.9 Hz, 2H), 1.66 – 1.59 (m, 2H), 1.44 – 1.33 (m, 5H), 0.92 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6 (C), 161.6 (C), 159.3 (C), 144.9 (C), 134.2 (C), 132.0 (CH), 129.5 (CH), 129.4 (CH), 129.2 (C), 128.6 (C), 128.3 (CH), 124.5 (C), 114.2 (CH), 103.2 (CH), 61.4 (CH_2), 55.2 (CH_3), 51.1 (CH_2), 34.0 (CH_2), 33.3 (CH_2), 22.6 (CH_2), 14.2 (CH_3), 13.8 (CH_3).

HMRS (ESI) calculated for $C_{24}H_{27}NO_4Na$ $[M+Na]^+$ 416.1832, found 416.1838.

2-Methyl-1-(1-(phenylsulfonyl)-*1H*-pyrrol-2-yl)propan-1-one: (2.35c)



$C_{14}H_{15}NO_3S$

To a stirred solution of *iso*-butyric anhydride (3.57 g, 3.74 mL, 22.56 mmol) in dry 1,2-dichloroethane (75 mL) was added boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$; 6.40 g, 5.72 mL, 45.11 mmol). The reaction mixture was left to stir at rt for 10 minutes before the addition of 1-phenylsulfonyl-*1H*-pyrrole **2.23** (4.25 g, 20.51 mmol) in dry 1,2-dichloroethane (20 mL). The resultant solution was allowed to stir for a further 8 hours. Subsequently, it was poured into a mixture of ice and water and the product was extracted twice with diethyl ether. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a brown liquid. The crude product **2.35c** was purified by flash chromatography on a silica gel column eluting with 10% ethyl acetate in petroleum ether to give the title compound **2.35c** (4.72 g, 83%) as a brown oil.

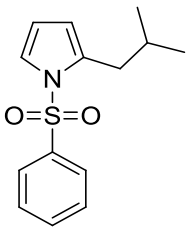
IR (neat) *v* (cm^{-1}) 3150, 2972, 2877, 1673, 1542, 1467, 1436, 1400, 1364, 1247, 1168, 1141, 1088.

^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 2H), 7.80 (dd, *J* = 1.6, 3.1 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H), 7.01 (dd, *J* = 1.5, 3.6 Hz, 1H), 6.34 (t, *J* = 3.5 Hz, 1H), 3.20 – 3.11 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2 (C), 139.1 (C), 133.4 (CH), 133.0 (C), 129.9 (CH), 128.6 (CH), 128.0 (CH), 122.3 (CH), 110.3 (CH), 37.0 (CH), 19.1 (CH_3).

HMRS (ESI) calculated for $C_{14}H_{15}NO_3SNa$ $[M+Na]^+$ 300.0664, found 300.0675.

2-Isobutyl-1-phenylsulfonyl-*1H*-pyrrole: (2.36c)



$C_{14}H_{17}NO_2S$

To a stirred suspension of aluminium chloride (5.77 g, 43.27 mmol) in dry CH_2Cl_2 (80 mL) was added borane *tert*-butylamine complex (*t*-$BuNH_2 \cdot BH_3$; 7.52 g, 86.54 mmol). The reaction mixture was left to stir at rt for 2 hours before the addition of 2-methyl-1-(1-(phenylsulfonyl)-*1H*-pyrrol-2-yl)propan-1-one **2.35c** (4.0 g, 14.42 mmol) in dry CH_2Cl_2 (20 mL). The resultant solution was allowed to stir for a further 16 hours. Subsequently, it was poured into a mixture of ice and water and the product was extracted twice with diethyl ether. The organic layers were combined, washed once with 3.0 M aqueous HCl solution, washed once with saturated aqueous $NaHCO_3$ solution, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow solid. The crude product **2.36c** was purified by flash chromatography on a silica gel column eluting with 15% diethyl ether in petroleum ether to give the title compound **2.36c** (3.8 g, 91%) as off white solid.

m p.: 62.1 - 64.0 °C

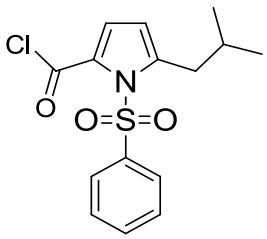
IR (neat) ν (cm^{-1}) 3152, 2956, 2870, 1571, 1446, 1390, 1358, 1296, 1332, 1183, 1144, 1047.

^{1}H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 7.74 (d, J = 7.9 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.30 (br s, 1H), 6.22 (t, J = 3.0 Hz, 1H), 6.00 (br s, 1H), 2.54 (d, J = 7.0 Hz, 2H), 1.94 – 1.85 (m, 1H), 0.87 (d, J = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7 (C), 135.1 (C), 133.5 (CH), 129.2 (CH), 126.4 (CH), 122.4 (CH), 113.3 (CH), 111.5 (CH), 36.3 (CH_2), 28.1 (CH), 22.3 (CH_3).

HMRS (ESI) calculated for $C_{14}H_{17}NO_2SNa$ $[M+Na]^+$ 286.0872, found 286.0883.

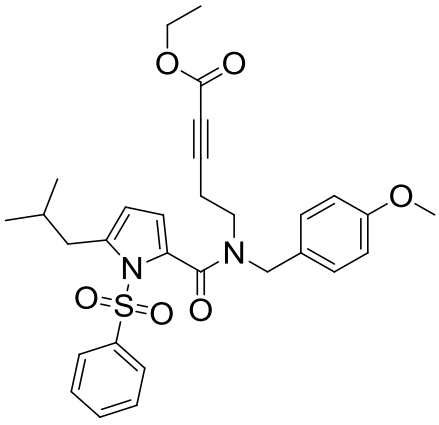
5-Isobutyl-1-phenylsulfonyl-*1H*-pyrrole-2-carbonyl chloride: (2.37c)



$C_{15}H_{16}ClNO_3S$

To a stirred suspension of aluminium chloride (3.04 g, 22.78 mmol) in dry 1,2-dichloroethane (50 mL) at 0 °C was added oxalyl chloride (2.89 g, 1.95 mL, 22.78 mmol). The reaction was left to stir for 30 minutes at 0 °C before the addition of 2-*iso*butyl-1-phenylsulfonyl-*1H*-pyrrole **2.36c** (1.2 g**,** 4.56 mmol) in dry 1,2-dichloroethane (15 mL). The resultant solution was allowed to warm to rt and left to stir for 2 hours. Subsequently, it was poured into a mixture of ice and water and the product was extracted twice with diethyl ether. The organic layers were combined, washed once with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a brown oil (1.41 g, 95%). The crude product **2.37c** was used directly in the next step without further purification.

Ethyl 5-(5-isobutyl-*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-*1H*-pyrrole-2-carboxamido)pent-2-ynoate: (2.38c)



$C_{30}N_{34}N_2O_6S$

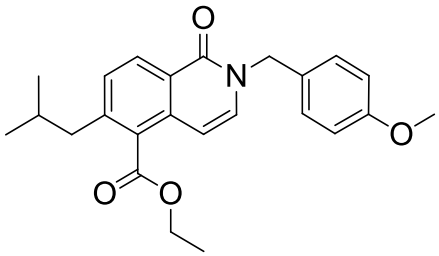
To a stirred solution of free base of amine **2.25** (1.25 g, 4.77 mmol) and triethylamine (0.88 g, 1.21 mL, 8.68 mmol) in dry THF (20 mL) at 0 °C was added acid chloride **2.37c** (1.41 g, 4.34 mmol) in dry THF (10 mL). The reaction was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched with water, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a dark yellow oil. The crude product **2.38c** was purified by flash chromatography on a silica gel column eluting with 40% diethyl ether in hexanes to give the title compound **2.38c** (2.15 g, 90%) as a pale yellow foam.

^{1}H NMR (500 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 8.15 (d, *J* = 7.9 Hz, 1.4H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 1.4H), 6.91 – 6.86 (m, 1.4H), 6.31 (d, *J* = 3.4 Hz, 0.7H), 5.94 (d, *J* = 3.3 Hz, 0.7H), 4.55 (s, 1.4H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 2.1H), 3.58 (br s, 1.4H), 2.68 (t, *J* = 7.0 Hz, 1.4H), 2.58 – 2.48 (m, 2H), 1.80 – 1.70 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.79 (d, *J* = 6.5 Hz, 6H); *Rotamer B*; 8.18 (d, *J* = 7.7 Hz, 0.6H), 7.35 (d, *J* = 8.4 Hz, 0.6H), 6.91 – 6.86 (m, 0.6H), 6.34 (d, *J* = 3.3 Hz, 0.3H), 5.98 (d, *J* = 3.1 Hz, 0.3H), 4.76 (s, 0.6H), 3.73 (s, 0.9H), 3.47 (t, *J* = 6.8 Hz, 0.6H), 2.58 – 2.48 (m, 0.6H).

^{13}C NMR (126 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 164.7 (C), 159.3 (C), 153.4 (C), 138.8 (C), 136.9 (C), 134.0 (CH), 129.4 (C), 129.2 (CH), 128.9 (CH), 128.0 (C), 127.6 (CH), 114.2 (CH), 112.7 (CH), 112.2 (CH), 86.6 (C), 74.1 (C), 61.7 (CH_2), 55.2 (CH_3), 52.7 (CH_2), 42.5 (CH_2), 36.5 (CH_2), 28.0 (CH), 22.3 (CH_3), 16.4 (CH_2), 13.9 (CH_3); *Rotamer B*; 164.9 (C), 159.1 (C), 153.2 (C), 138.7 (C), 137.2 (C), 129.7 (CH), 128.4 (C), 127.6 (CH), 114.0 (CH), 113.4 (CH), 112.4 (CH), 85.2 (C), 74.6 (C), 61.8 (CH_2), 55.1 (CH_3), 47.5 (CH_2), 45.6 (CH_2), 36.6 (CH_2), 28.1 (CH), 18.3 (CH_2).

HMRS (ESI) calculated for $C_{30}H_{34}N_2O_6SNa$ $[M+Na]^+$ 573.2030, found 573.2002.

Ethyl 6-isobutyl-2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisoquinoline-5-carboxylate: (2.39c)



$C_{24}H_{27}NO_4$

To a stirred solution of amide **2.38c** (1.5 g, 2.72 mmol) in anhydrous pyridine (30 mL) was added lithium iodide (0.36 g, 2.72 mmol). The mixture was heated at reflux for 8 hours, cooled to rt and diluted with CH_2Cl_2. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with CH_2Cl_2. The organic layers were combined, washed once with saturated aqueous $NaHCO_3$ solution, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow solid. The crude product **2.39c** was purified by flash chromatography on a silica gel column eluting with 50% diethyl ether in hexanes to give the title compound **2.39c** (0.57 g, 54%) as a white solid.

m.p : 65.1 - 65.8 °C

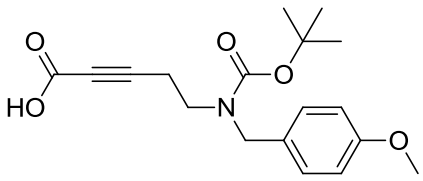
IR (neat) *v* (cm^{-1}) 2956, 2922, 2857, 1721, 1650, 1624, 1587, 1512, 1461, 1368, 1327, 1300, 1247, 1174, 1122, 911, 848, 817, 776, 727.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.45 (d, *J* = 7.6 Hz, 1H), 5.13 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 2.64 (d, *J* = 7.3 Hz, 2H), 2.00 – 1.90 (m, 1H), 1.41 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6 (C), 161.6 (C), 159.3 (C), 143.7 (C), 134.2 (C), 132.0 (CH), 129.7 (CH), 129.4 (CH), 129.1 (C), 128.9 (C), 128.7 (CH), 124.6 (C), 114.2 (CH), 103.2 (CH), 61.4 (CH_2), 55.2 (CH_3), 51.1 (CH_2), 43.1 (CH_2), 30.0 (CH), 22.4 (CH_3), 14.2 (CH_3).

HMRS (ESI) calculated for $C_{24}H_{27}NO_4Na$ $[M+Na]^+$ 416.1832, found 416.1829.

5-((*tert*-butoxycarbonyl)(4-methoxybenzyl)amino)pent-2-ynoic acid (2.40)



$C_{18}H_{23}NO_5$

To a stirred solution of ethyl ester **2.21** (201 mg, 0.56 mmol) in MeOH (3 mL) was added 20% aqueous KOH solution (20% w/v, 38 mg, 0.19 mL) at 0 °C. The reaction was allowed to warm to rt and left to stir for 2 days. The reaction mixture was then poured into ice-water and the aqueous layer washed with CH_2Cl_2. The aqueous layer was then acidified (pH 1) with 3M HCl solution and extracted with CH_2Cl_2. The organic fractions were combined and extracted with saturated aqueous $NaHCO_3$ solution. The combined aqueous layer was acidified (pH 1) with 3M HCl and aqueous layer extracted with CH_2Cl_2. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a colourless oil (110 mg, 62%). The crude product **2.40** was used directly in the next step without further purification.

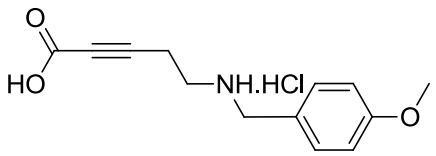
IR (neat) ν (cm^{-1}) 3417, 2977, 2934, 2237, 1691, 1612, 1513, 1413, 1367, 1248, 1162.

^{1}H NMR (300 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 9.49 (br s, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 4.38 (s, 1.4H), 3.72 (s, 3H), 3.32 – 3.24 (m, 2H), 2.46 – 2.38 (m, 2H), 1.44 (s, 9H); *Rotamer B*; 4.30 (s, 0.6H)

^{13}C NMR (75.5 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 157.9 (C), 155.5 (C), 154.0 (C), 128.8 (C), 128.0 (CH), 114.0 (CH), 86.5 (C), 80.3 (C), 74.7 (C), 54.6 (CH_3), 50.1 (CH_2), 43.7 (CH_2), 28.0 (CH_3), 17.3 (CH_2); *Rotamer B*; 129.0 (C), 128.2 (CH), 53.7 (CH_3), 48.9 (CH_2), 43.5 (CH_2), 17.5 (CH_2).

HMRS (ESI) calculated for $C_{18}H_{23}NO_5Na$ $[M+Na]^+$ 356.1462, found 356.1462.

5-((4-methoxybenzyl)amino)pent-2-ynoic acid hydrochloride (2.41)



$C_{13}H_{16}ClNO_3$

To a stirred solution of carboxylic acid **2.40** (513 mg, 1.32 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added a 4M solution of HCl in dioxane (8 mL, 32.0 mmol). The reaction was allowed to warm to rt and left to stir for 16 hours, during which time the formation of white precipitates were observed. The solvent was removed *in vacuo* to afford a pale brown solid. This solid was triturated with diethyl ether to afford a white solid which was collected by filtration and washed well with diethyl ether, after drying under high vacuum the title product obtained was a white solid. The crude product **2.41** was used directly in the next step without further purification (275 mg, 82%).

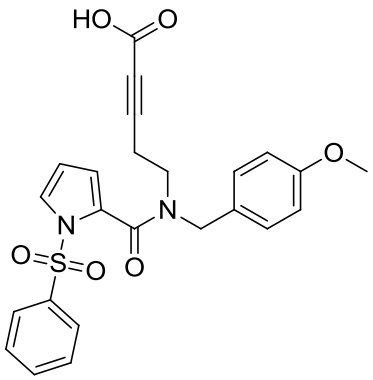
IR (neat) ν (cm^{-1}) 2924, 2854, 2246, 1692, 1460, 1143, 1253, 1178, 1032.

^{1}H NMR (300 MHz, $CDCl_3$, broadened signals were observed) δ 9.64 (br s, 1H), 7.50 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 4.10 (s, 2H), 3.77 (s, 3H), 3.20 – 3.00 (m, 2H), 2.98 – 2.80 (m, 2H).

^{13}C NMR (75.5 MHz, DMSO-d_6) δ 160.0 (C), 154.1 (C), 132.0 (C), 123.9 (CH), 114.3 (CH), 83.7 (C), 75.9 (C), 55.5 (CH_3), 49.6 (CH_2), 43.9 (CH_2), 15.7 (CH_2).

HMRS (ESI) calculated for $C_{13}H_{15}NO_3Na$ $[M\text{-}HCl+Na]^+$ 256.0950, found 256.0966.

5-(*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-*1H*-pyrrole-2-carboxamido)pent-2-ynoic acid: (2.10)



$C_{24}H_{22}N_2O_6S$

To a stirred solution of salt **2.41** (187 mg, 0.69 mmol) and triethylamine (147 mg, 0.20 mL, 1.45 mmol) in dry THF (5 mL) at 0 °C was added acid chloride **2.24** (186 mg, 0.66 mmol) in dry THF (5 mL). The reaction was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched with water, the aqueous layer was acidified and extracted three times with CH_2Cl_2. The organic layers were combined, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a pale yellow oil. The crude product **2.10** was purified by flash chromatography on a silica gel column eluting with 1% methanol in CH_2Cl_2 to give the title compound **2.10** (135 mg, 44%) as a yellow oil.

IR (neat) ν (cm^{-1}) 3065, 2932, 2239, 1712, 1612, 1514, 1369, 1249, 1176, 1154.

^{1}H NMR (300 MHz, $CDCl_3$, resolved signals of rotamers) δ *Rotamer A*; 8.04 (d, *J* = 7.0 Hz, 2H), 7.66 – 7.49 (m, 3H), 7.27 – 7.22 (m, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.34 (br s, 0.7H), 6.23 (br s, 0.7H), 4.55 (s, 1.4H), 3.80 (s, 3H), 3.60 (t, *J* = 7.0 Hz, 1.4H), 2.72 (t, *J* = 7.0 Hz, 1.4H); *Rotamer B*; 6.40 (br s, 0.3H), 6.28 (br s, 0.3H), 4.78 (s, 0.6H), 3.48 (br s, 0.6H), 2.52 (br s, 0.6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.5 (C), 159.8 (C), 156.4 (C), 138.7 (C), 134.7 (CH), 129.6 (CH), 129.2 (CH), 128.3 (CH), 127.9 (C), 123.4 (CH), 114.6 (CH), 114.5 (CH), 112.7 (CH), 86.8 (C), 74.6 (C), 55.7 (CH_3), 53.5 (CH_2), 43.0 (CH_2), 17.3 (CH_2).

HMRS (ESI) calculated for $C_{24}H_{22}N_2O_6SNa$ $[M+Na]^+$ 489.1091, found 489.1092.

Chapter 5.

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Part 2

Investigation and Development of a Novel Cascade Reaction

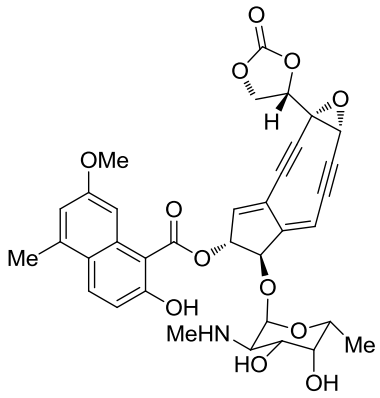
Chapter 1.
Introduction

1.1. Metal-Free Methods of Generating Diradicals

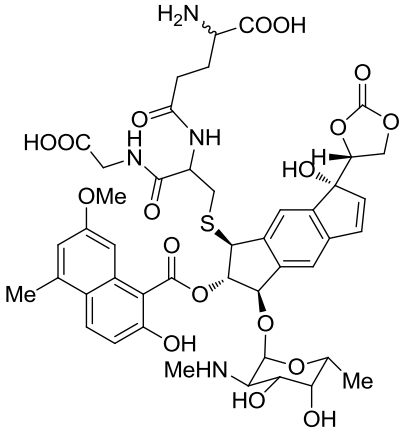
1.1.1. Natural Enediyne Anticancer Antibiotics

The enediyne antibiotics are amongst the world's most powerful antitumor agents, due to their intense activity against a multitude of murine tumour models.[1] These compounds exhibit a new class of antibiotic with an exclusive chemical architecture, in which all members comprise a unit with two acetylenic groups adjoined to a double bond or incipient double bond with a nine or ten-membered ring.[2] In the presence of DNA, enediyne antibiotic undergoes a prominent reaction, yielding sp^2 carbon centred diradicals as the biologically active species.[3] Nevertheless, the enediyne natural products are not discerning in their activity and will cleave DNA in both healthy and cancerous cells. This unselective behaviour has incited a concentration of experimental[4] and computational[5] research aimed at rational drug design.

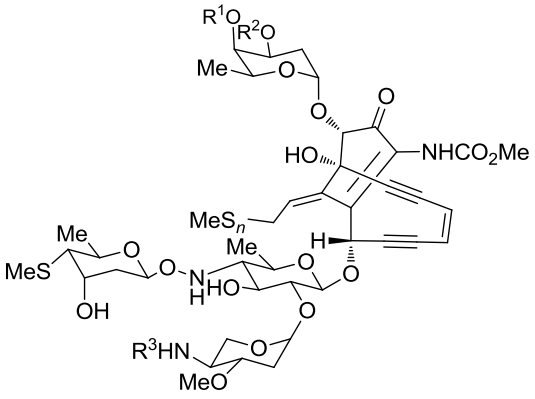
To date, there are three distinct families within the enedyine antibiotic class. These are defined as the following types; 1-) calicheamicin/esperamicin, 2-) dynemicin and 3-) chromoprotein. The original members identified of this new class were calicheamicin and esperamicin. These two antibiotics occur as complexes of several closely related components. The family of enediynes represented by chromoproteins used to be designated as neocarzinostatin.



Neocarzinostatin **(1.1)**



Post activated neocarzinostatin **(1.2)**



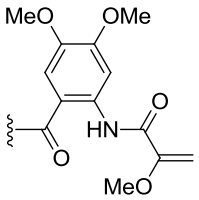
n = 3, 4

R^1 = H, Ar

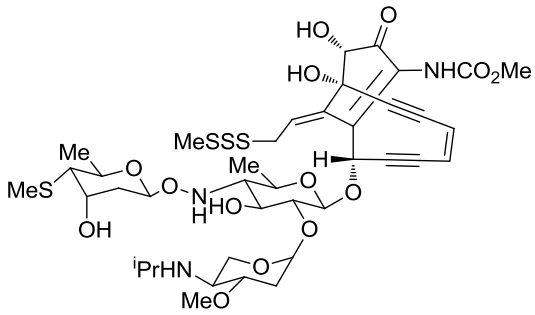
R^2 = Ar, H

R^3 = *i*-Pr, Me, Et

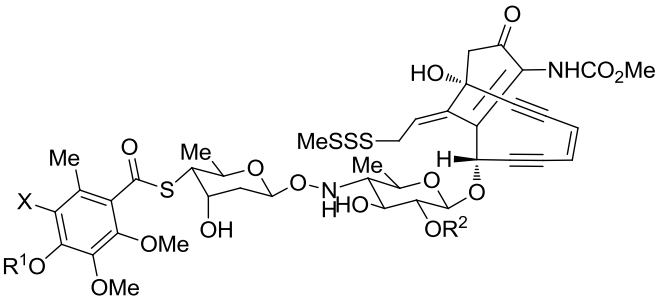
Ar =



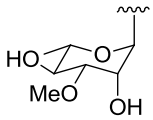
Esperacmicin **(1.3)**



Esperacmicin C **(1.4)**

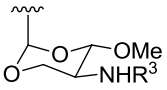


R^1 = H,



3-*O*-MeRha

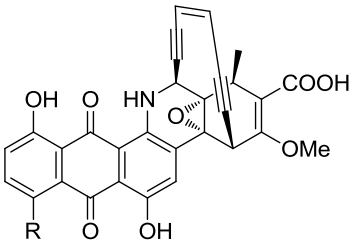
R^2 = H,



Ami

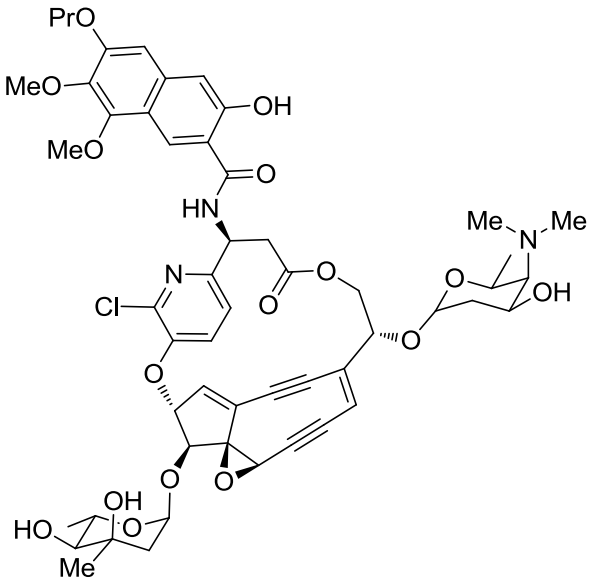
R^3 = Me, Et, *i*-Pr

Calicheamicin **(1.5)**



Dynemicin A **(1.6)** R = OH

Deoxydynemicin A **(1.7)** R = H



Kadercidin **(1.8)**

Figure 1.1: The Key Enediyne Antitumor Antibiotics

The enediyne antibiotics were originally produced from the fermentation of microorganisms. The organisms found to render the various enediyne complexes include different species *Micromonospora*, *Actinomadura* and *Steptomyces.* In account of their capacity to cleave DNA *via* the proposed Bergman cyclisation, much attention has been given to the enediyne compounds as potential sources for anticancer therapeutics.[6]

To date, there have been many natural enediynes isolated from various marine and terrestrial plant sources. These represent highly potent clinically established classes of antitumor, antimicrobial and cytotoxic agents. Neocarzinostatin chromophores (**1.1** and **1.2**), esperamicins (**1.3** and **1.4**), calicheamicin (**1.5**), dynemicins (**1.6** and **1.7**), kedarcidin (**1.8**), N1999-A2 (**1.26**), maduropeptin (**1.27**), shishijimicins (**1.30A-C**), namenamicin (**1.31**), lidamicins (C-1027) (**1.32**) and recently found uncialamycin (**1.28** and **1.29**) are the commonly known natural enediynes. Total syntheses of natural enediynes brought solutions for many challenging molecular architectures and made a distinct contribution to the progress of synthetic methodologies.[7] Apart from their biological activity, enediynes are key building blocks in the synthesis of helical polycyclic aromatic hydrocarbons and of particular interest on account of their optical and electronic properties.[8] In addition to this, it was suggested that enediynes are potentially useful mechanophores; that is, stress-sensitive units applied to the synthesis of polymers whose properties can be altered by mechanical energy.[9]

1.1.1.1. *Calicheamicin and Esperamicin*

The cyclic ten-membered enediyne esperamicins (**1.3** and **1.4**) were isolated from a fermentation broth of *Actinomadura* V*errucosospora* in 1985.[10] Subsequently, their structures were reported two years later;[11] the precise mechanism for esperamicin A_1's antitumor activity is not entirely understood. In a recent paper by Capitani *et al.*,[12] a number of explanations are brought to light. In the most widely acknowledged mechanism for esperamicin's activity, a bioreductive cleavage of the trisulfide tail, is conducted by a reducing agent formulating a thiol.[13] The thiol is then subjected to an intramolecular accumulation to the ten-membered ring comprising of the enediyne moiety. This in turn decreases differential strain between the reactant and intermediate state and increases flexibility in the enediyne ring, which considerably drops the activation barrier for Bergman cyclisation.

Esperamicin	*n*	R^1	R^2	R^3
Esperamicin A_1	3	H	Ar	*i*-Pr
Esperamicin A_{1b}	3	Ar	H	*i*-Pr
Esperamicin A_{1c}	3	H	Ar	Me
Esperamicin P	4	H	Ar	*i*-Pr
Esperamicin A_2	3	H	Ar	*i*-Pr
Esperamicin A_{2b}	3	Ar	H	Et
Esperamicin A_{2c}	3	Ar	H	Me

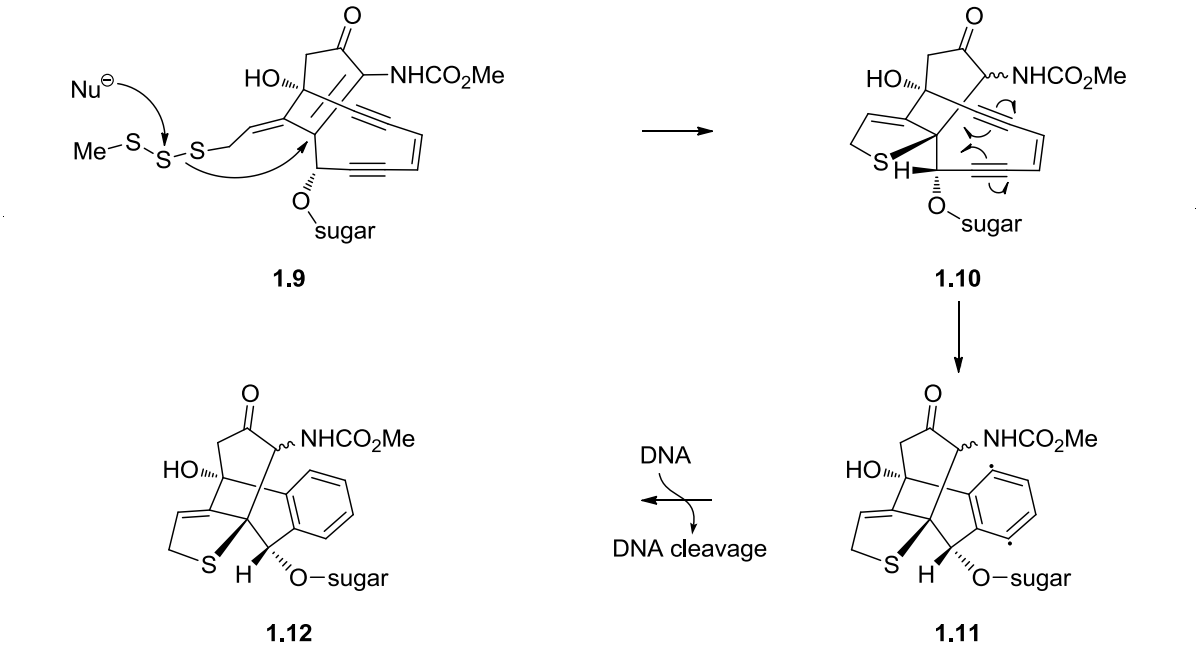
Table 1.1: Enediyne Esperamicins

The cyclic ten-membered enediyne calicheamicins **1.5** were isolated from the soil bacterium Micromonospora echinospora spp. calichensis in 1986.[14] Initially, the structure was put forward by Lee *et al.*[14] in 1987. Subsequently, a revision of the configuration at one of the stereogenic centres took place. The total synthesis was then accomplished by Nicolaou and Dai.[15]

Calicheamicin	X	R^1	R^2	R^3
Calicheamicin β_1^{Br}	Br	3-*O*-MeRha	Ami	Me_2CH
Calicheamicin γ_1^{Br}	Br	3-*O*-MeRha	Ami	Et
Calicheamicin α_1^{I}	I	H	Ami	Et
Calicheamicin α_3^{I}	I	3-*O*-MeRha	H	-
Calicheamicin β_1^{I}	I	3-*O*-MeRha	Ami	Me_2CH
Calicheamicin γ_1^{I}	I	3-*O*-MeRha	Ami	Et
Calicheamicin δ_1^{I}	I	3-*O*-MeRha	Ami	Me

Table 1.2: Enediyne Calicheamicins **1.5**

Calicheamicin γ1 is one of the most prominent components of the calicheamicin complex. The enediynes Calicheamicin γ1 and esperamicin A_1 share the same amino sugars, thio sugar and enediyne chromophore with a methyl trisulfide group. However, there is a difference in substitution alongside the keto group of the chromophore, the substitution of the aromatic groups, the composition of substituent sugar and aromatic units of the chromophore. Despite differences in structure between both molecules, they cleave DNA *via* the equivalent free radical mechanism (**Scheme 1.1**).

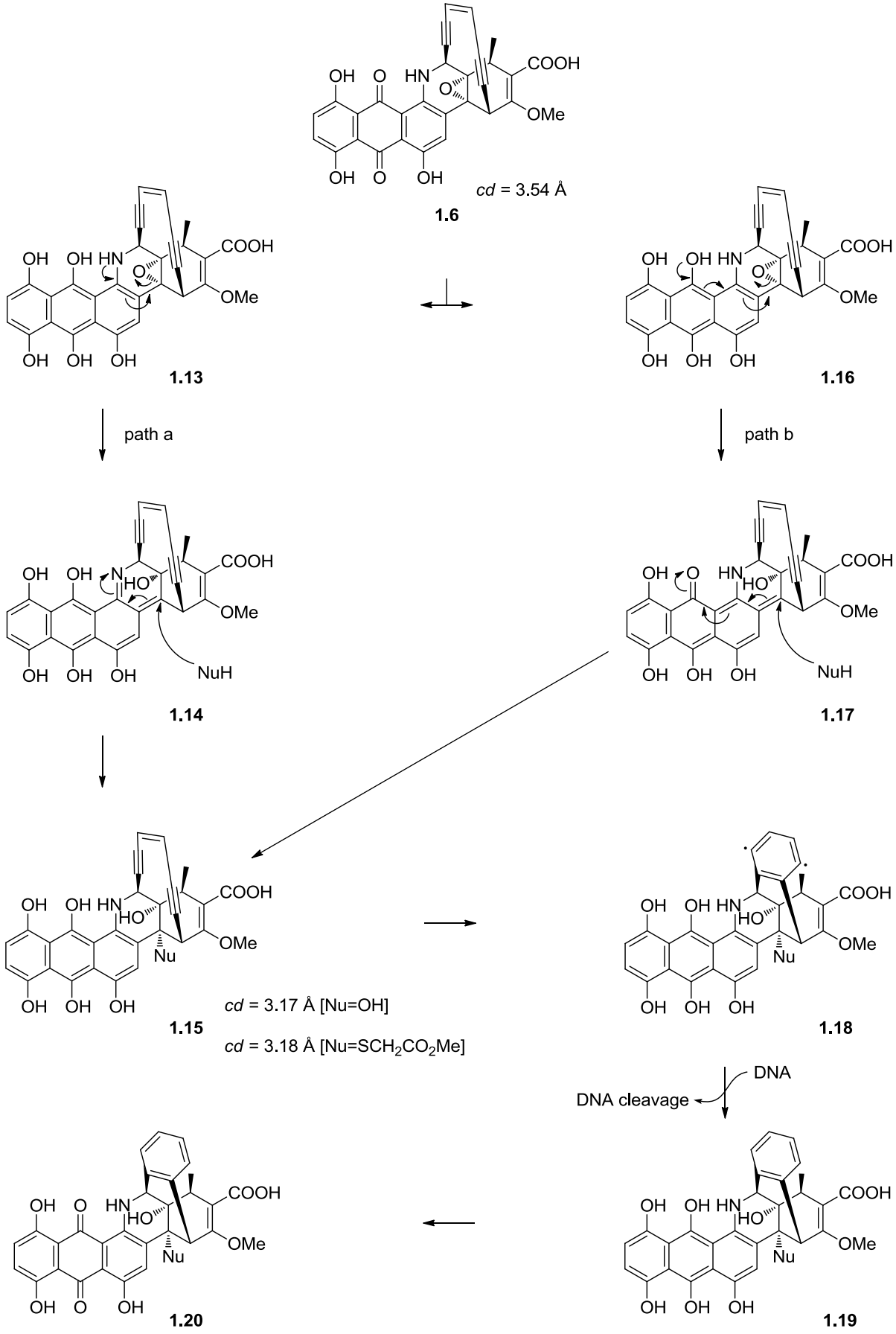


Scheme 1.1: The Mechanism of DNA Cleavage by Calicheamicin γ1

1.1.1.2. *Dynemicin*

The prominent component of the complex was named dynemicin A **1.6**, discovered in 1989 when it was isolated from a fermentation broth of *Micromonospora chersina*.[16,17] This highly effective antitumor antibiotic has a ten-membered enediyne unit linked with the hydroxyanthraquinone chromophore of the classical anthracycline antibiotics. The existence of the anthraquinone moiety in the molecule is in disparity to the other members of the family such as calicheamicin $\gamma 1$ and esperamicin A_1, which have oligosaccharide tails.[5] It is this contrast which makes **1.6** a particularly interesting contender for quantum chemical studies as its structure is both relatively inflexible and condensed. Furthermore, it has been the subject of extensive investigation by synthetic chemists. Investigations have been predominantly focused on the active centre, such as the pentacyclic framework and enediyne core.[18] Following this, Myers *et al.*[19] accomplished a highly-convergent enantioselective synthesis of dynemicin A **1.6** in 1995.

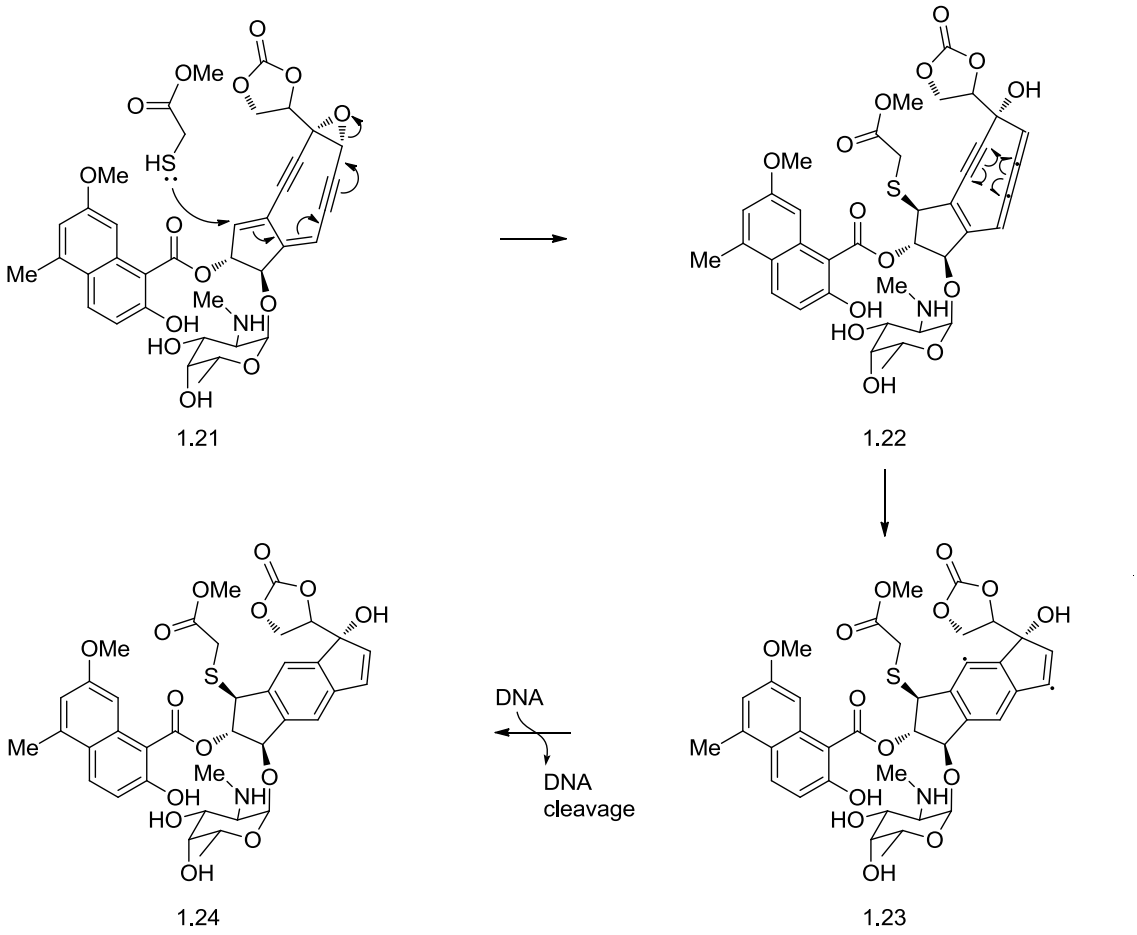
More recently, an additional member of this family, bioactive deoxydynemicin A **1.7**, was isolated from *Micromonospora globosa* MG331-hF6.[20] Similar to the activity of dynemicin A **1.6**, this member cleaves DNA duplex causing both single- and double-stranded cuts. Several dynemicin A model systems were designed, synthesised and investigated by Nicolaou *et al.*[21] As a response to these investigations, the cascade through a hetero atom mediated epoxide ring opening was hypothesised. More specifically, two mechanisms were put forward (**Scheme 1.2**). Intercalation of the anthracycline like aromatic backbone followed by bioreduction, renders the dihydroanthroquinone **1.13**.[22] Heteroatom-mediated epoxide ring opening[21,23,24] initiated by either the hydroquinone (path b)[22,25] or the secondary amine (path a)[21,26,27] yields the quinone **1.17** or imine **1.14** respectively. Nucleophilic attack on either intermediate renders the same re-aromatised product **1.15** with a greatly reduced *cd* distance (3.17 Å [Nu=OH, MMX], 3.18 Å [Nu=SCH_2CO_2Me. MMX]). [28] A spontaneous Bergman cyclisation then occurs in the aromatised precursor **1.15** to produce the bi-radical species **1.18**. This is comparable to that previously seen in the esperamicins (esperamicin A_1) and calicheamicins (calicheamicin γ_1) and leads to the duplex cleavage of DNA. The formulation of **1.19** *via* the process of DNA cleavage is subsequently oxidised and produces the anthroquinone product **1.20**.



Scheme 1.2: The Mechanism of DNA Cleavage by Dynemicin

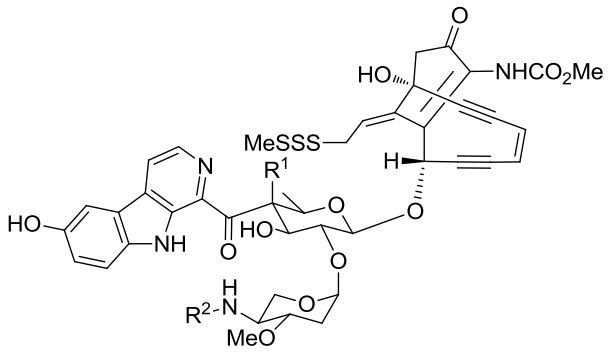
1.1.1.3. *Neocarzinostatin Chromophore*

Chromoproteins are a category of potent antitumor antibiotics that comprise of a non-peptidic chromophore complexed with an apoprotein. These antibiotics commonly contain broad-spectrum antitumor activity against solid-tumor cell lines. The intensely acidic protein provides stability to the chromophore from the generating organism and most likely, acts to protect the organism from DNA deterioration. Therefore, there has been substantial interest in establishing the tertiary structure of the apoproteins. This effort has acquired encouragement from the observation that the apoproteins of auromomycin (macromomycin) and actinoxanthin exhibit considerable resemblance to the apoprotein of neocarzinostatin.[29] Neocarzinostatin (NCS) was the first naturally occurring enediyne chromoprotein studied[30] and displays an interesting feature; its carrier protein is able to divert the enediyne cycloaromatisation into a distinct pathway. It has a unique double role in that it intercalates into DNA and imposes radical-mediated damage after thiol activation.[31]



Scheme 1.3: The Mechanism of DNA Cleavage by Neocarzinostatin

The mechanism of action for neocarzinostatin chromophore appeared similar to that of calicheamicin and esperamicin and it consisted of two acetylenic units in a nine-membered ring. Therefore, the neocarzinostatin chromophore was subsequently acknowledged as an additional member of the new enediyne class of antibiotics.

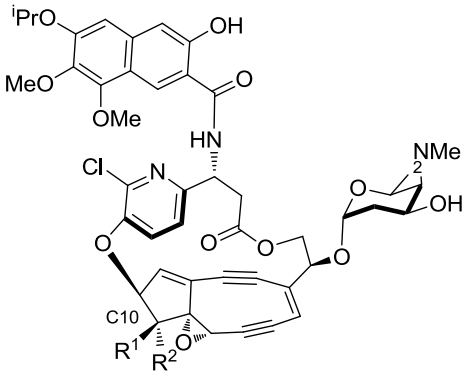


shishijimicins (**1.25A-C**)

(**1.25A**) : R^1 = SMe, R^2 = *i*-Pr

(**1.25B**) **:** R^1 = H, R^2 = *i*-Pr

(**1.25C**) **:** R^1 = SMe, R^2 = Et

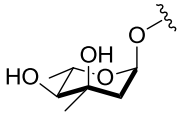


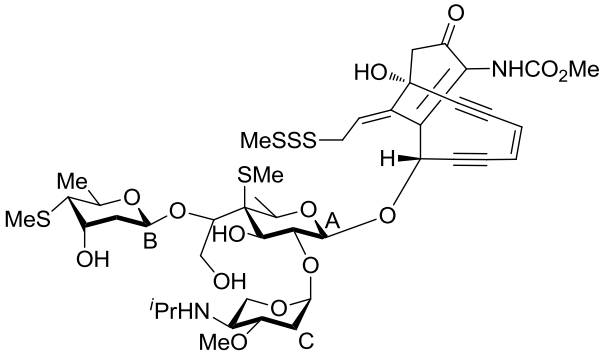
kedarcidin (**1.26-1.27**)

(**1.26**) : R^1 = H, R^2 = L-mycarose

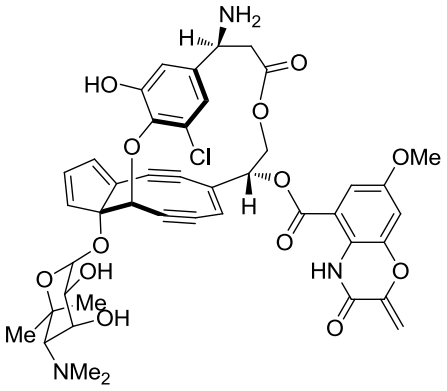
(**1.27**) : R^1 = L-mycarose, R^2 = H

L-mycarose =





Namenamicin (**1.28**)



C-1027 chromophore (**1.29**)

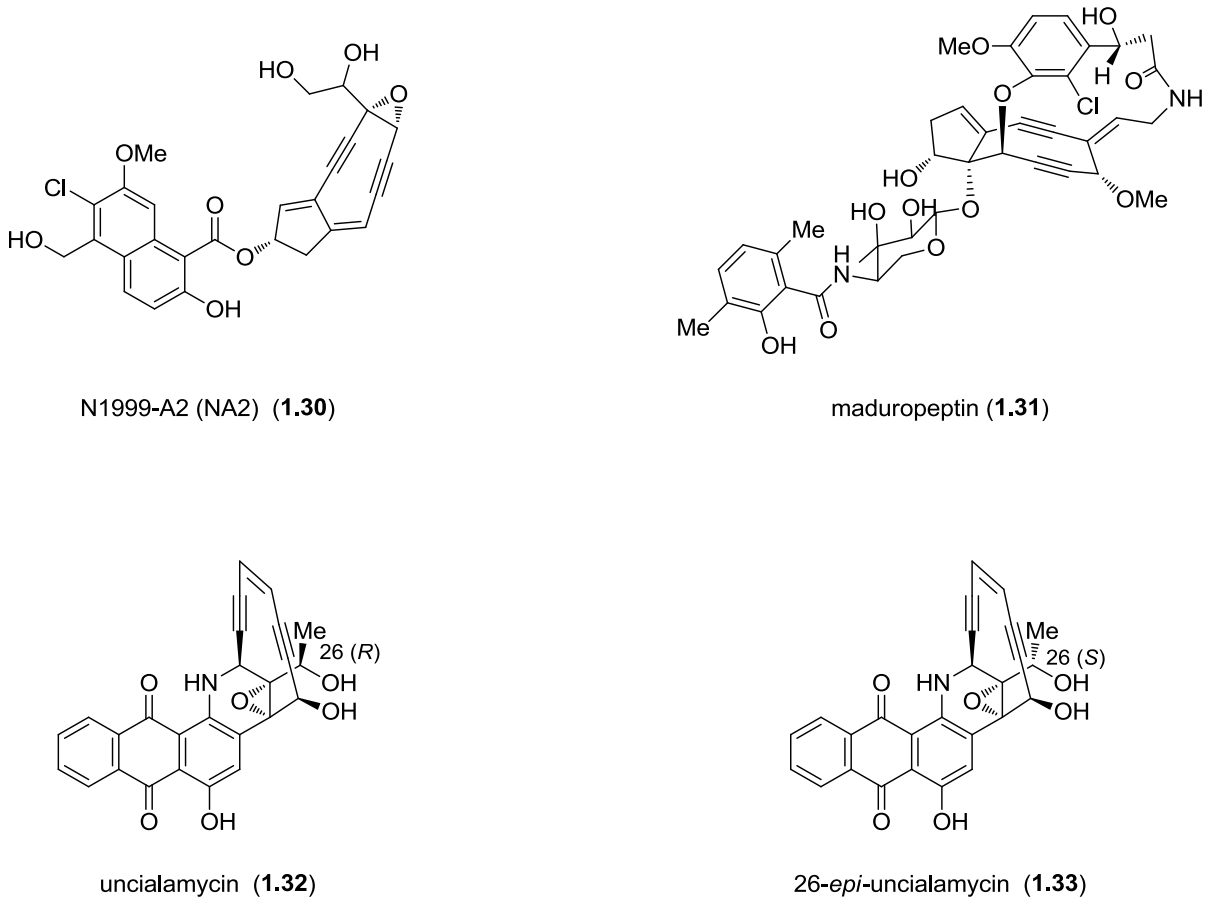


Figure 1.2: The Key Enediyne Antitumor Antibiotics

1.1.1.4. *Namenamicin and Shishijimicins*

The cyclic nine-membered enediyne namenamicin **1.28** is one of two enediyne natural products of marine origin. Isolated from the Fijian tunicate *Polysyncraton lithostrotum*, this enediyne was extracted in very low yield (less than 1 mg from 1 kg of frozen tissue, 0.0001% yield).[32] Strikingly, it has much in common with its nearby terrestrial equivalents, the calicheamicins **1.4** and esperamicins **1.3**. Similarities can be detected between its trisaccharide domain and esperamicin A_1, in particular the presence of isopropyl aminosugar (C ring) and two unusual 6-deoxysugars (A and B rings). However, namenamicin's most unusual feature is the novel linkage between the A and B rings in which C4 of the A ring is disubstituted with a methyl thioether and a two carbon moiety to which the B ring is adjoined at the C7 oxygen. As a result of its capacity to cleave DNA and its limited availability, Nicolaou *et al.*[33] reported progress towards the total synthesis of this natural product.

The on-going search for bioactive metabolites from Japanese marine invertebrates, led Fusetani *et al.*[34] to discover a lipophilic extract of ascidian *Didemnum proliferum* which showed cytotoxicity. Four active compounds were furnished as a result of Bioassay-guided isolation; the first was identified as namenamicin **1.28** by spectral data. The remaining three were novel compounds of the enediyne class named shishijimicins **1.25A-C** and these exhibited highly potent cytotoxicity. Additionally, Shishijimicins **1.25A-C** and namenamicin **1.28** are the only members of the enediyne class to derive from marine sources.

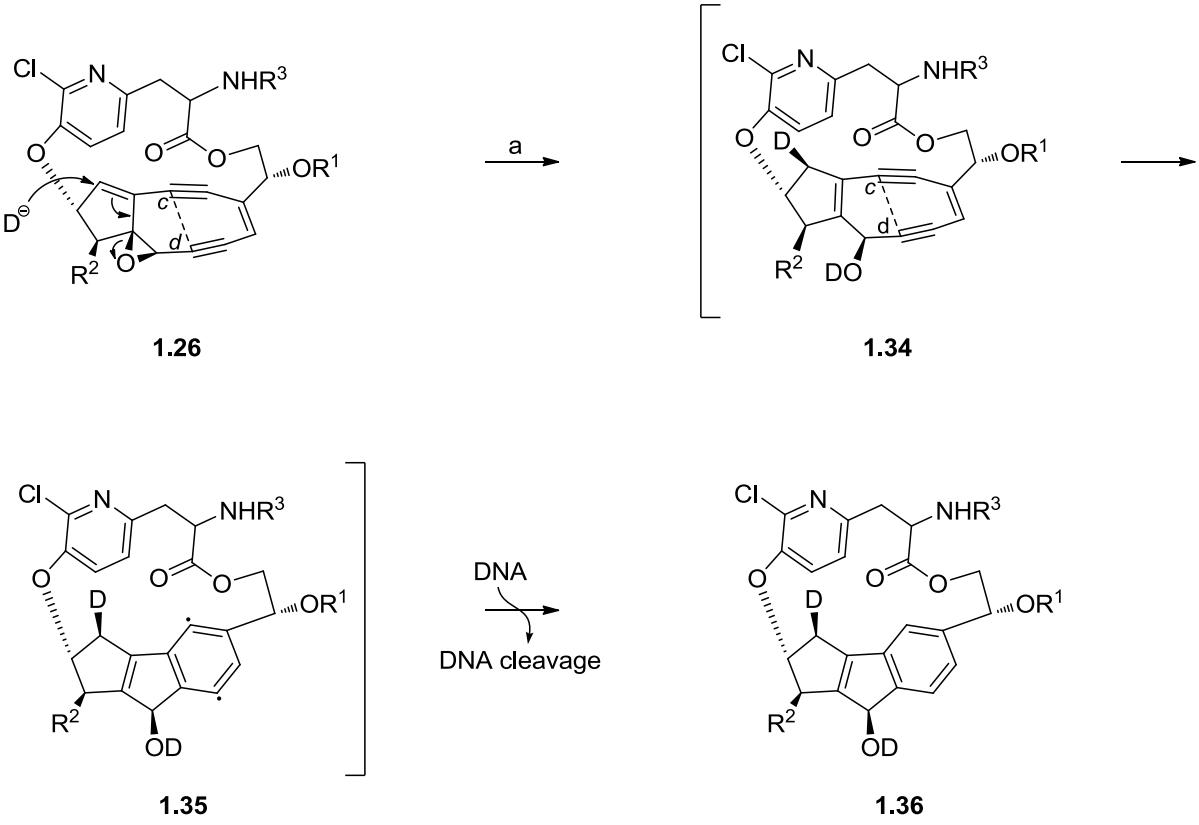
Each of the shishijimicins contains the equivalent enediyne core to the one detected in namenamicin **1.28** and calicheamicin γ1 (known as calicheamicinone) **1.4**. There is a distinct difference however, in the unique carboline structural motif of the shishijimicins. Respectively, *β*-carboline is reported to intercalate into double-stranded DNA[35] and numerous *β*-carbolines have been able to cleave DNA under photoirradiation conditions.[36] Also, Shishijimicin **1.25A** is the most potent of the shishijimicin family, in account of these findings and the extreme rarity of shishijimicin **1.25A**, Nicolaou *et al.*[37] recently reported the chemical synthesis of the carboline disaccharide domain of shishijimicin **1.25A**.

1.1.1.5. *Kedarcidin*

The structure of the cyclic nine-membered kedarcidin, an antitumor enediyne, was first reported in 1991 as fermentation product of *Actinomycete* strain (L585–6).[38] The enediyne antitumor antibiotic kedarcidin carries an intricate ansamacrocyclic bridge and two unique 2-deoxysugar components. This complex chemical architecture and high level of reactivity accounts for several revisions on the reported structure of kedarcidin.[39,40] Its structure was initially proposed by Leet *et al.* in 1992,[41] the α-azatyrosyl fragment of the ansa-bridge was then revised to the interrelated *β*-amino acid derivative. In addition, the definitive structure of the entire molecule was amended by Hirama *et al.* [42] as **1.26** in 1997 and the total synthesis of **1.26** was accomplished by Myers and coworkers in 2007.[43] As a result of the total synthesis of **1.26**, ^{1}H NMR data enabled a further revision of the C10 stereochemistry as illustrated in structure **1.27** (**Figure 1.2**).[43]

The work of Leet's group proposed that kedarcidin **1.26** functions differently compared with the enediyne triggers reported to date.[41] The identified *cd* distance in the stable enediyne has been determined at just 2.85 Å,

which is considerably lower than necessary for spontaneous cyclisation.[87,88] In light of this observation and the marginal decrease in the *cd* distance 2.82 Å upon epoxide opening, the role of the epoxide chemical protecting group is not to inhibit Bergman cyclisation by increasing the *cd* distance. Alternatively, it is understood that the role of the epoxide chemical protecting group is to increase the ring strain engaged with the transition states of the Bergman cyclisation and therefore, to counteract its occurrence. Deuterium labelled epoxide opening, afforded evidence for the theorised epoxide chemical protecting group (**Scheme 1.6**).



1.26 **1.34** **1.35** **1.36**

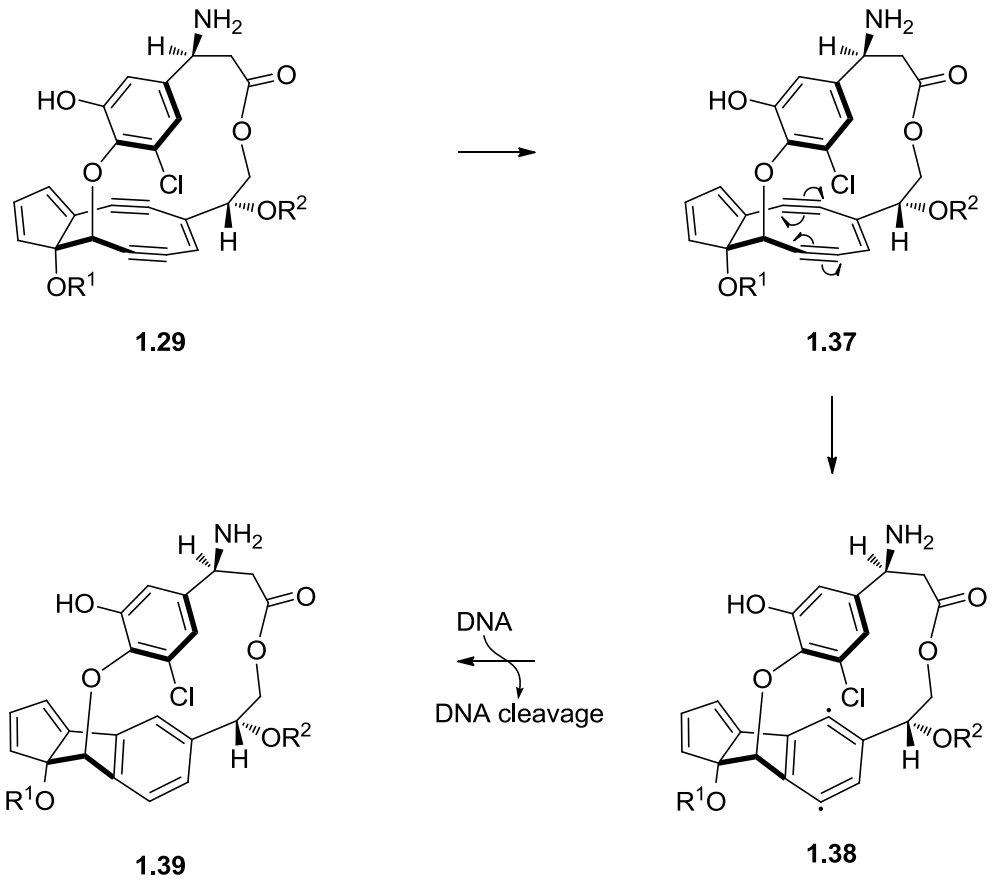
Reagents and Conditions: (a) $NaBD_4$, CD_3OD.

Scheme 1.6: Original Reaction Pathway Suggested by Leet *et al.*[41] (containing debated stereochemistry)

1.1.1.6. *C-1027 Chromophores*

In 1988, the cyclic nine-membered enediyne C-1027 chromophore **1.29** was isolated from culture filtrates of *Streptomyces globisporus*.[44] The C-1027 is a representative of potent

antitumor antibiotic chromoproteins and consists of a nonprotein chromophore and its carrier apoprotein.[45] The chromophore is very labile, but is considerably stabilised through specific binding to the apoprotein. If separated from the binding protein, the C-1027 chromophore **1.29** has very limited stability in solution and has been demonstrated to undergo spontaneous cycloaromatisation *via* Masamune–Bergman rearrangement. The nine-membered enediyne moiety of **1.29** is unlike all the other enediyne natural products reported, which depend on external activators such as nucleophiles to instigate the electronic rearrangement. Uniquely, the nine-membered enediyne moiety of **1.29** spontaneously aromatises at room temperature without the presence of an activator.[46] This high level of reactivity, alongside distinct structural features such as the chlorocatechol-containing ansa-bridge with atropisomerism, the highly strained bicyclo[7.3.0]trienediyne, the appended benzooxazine and the aminosugar present the inherent difficulty in achieving the total synthesis of **1.29**.[47]



Scheme 1.5: The Mechanism of DNA Cleavage by C-1027 Chromophore

1.1.1.7. *N1999-A2 (NA2)*

The novel antibiotic N1999-A2 (NA2) **1.30**, isolated from a culture supernatant of *Streptomyces* sp. AJ9493,[48] contains a naphthoate moiety and a nine-membered ring enediyne chromophore (**Figure 1.2**). The molecular structure of NA2 **1.30** is strikingly similar to that of neocarzinostatin chromophore (NCS-chr) **1.1** with the exception that neocarzinostatin chromophore consists of an aminoglycoside residue. NA2 **1.30** is adequately stable during the isolation process despite the non-protein chromophores and this is of particular interest and differs significantly from the other nine-membered ring enediyne chromophore.

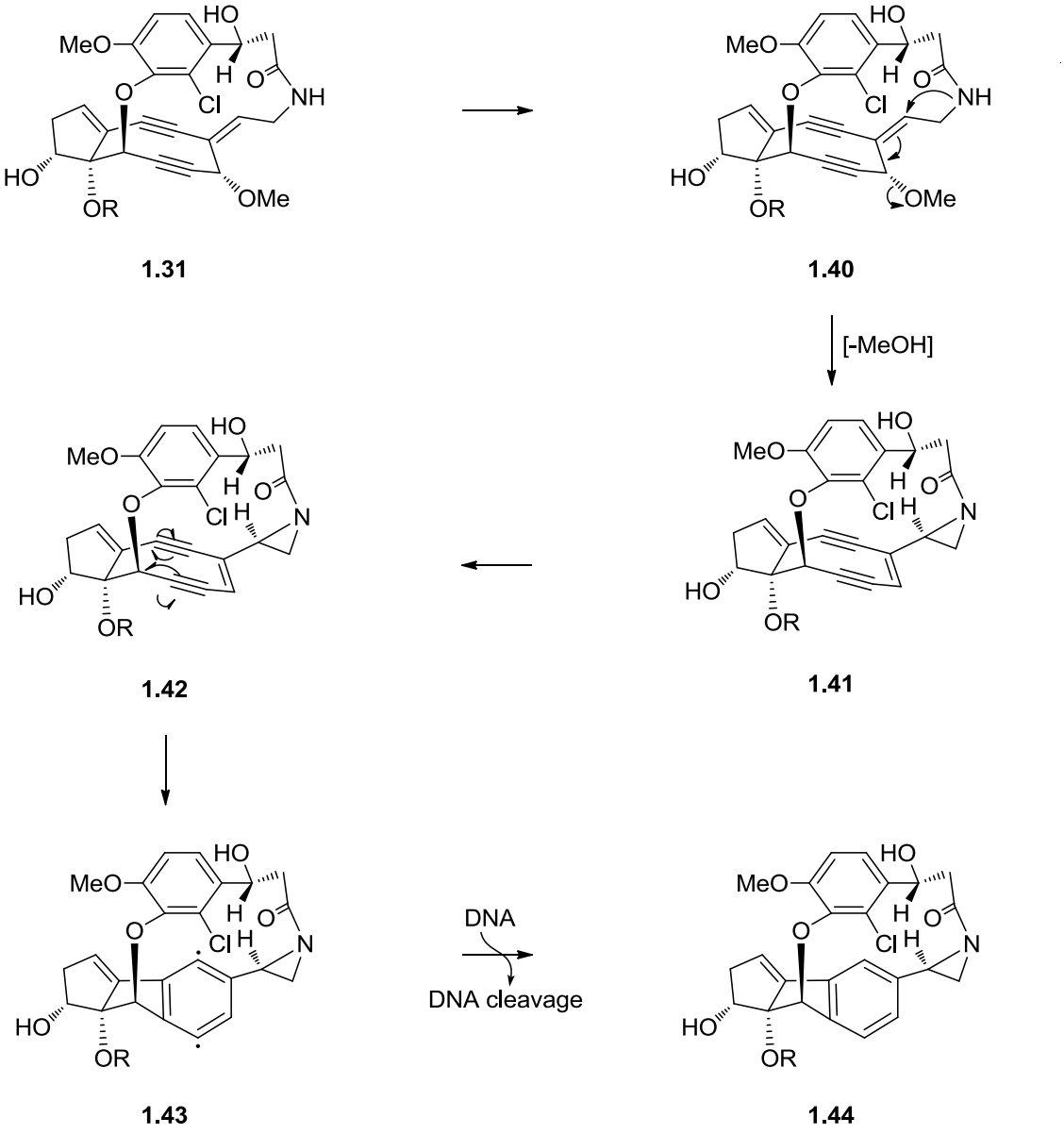
To further investigate the stability of NA2 **1.30** in solution, Miyagawa *et al*.[49] scrutinised the DNA cleavage activity of NA2 **1.30**. The results indicated that NA2 **1.30** was substantially stable at 37 °C and the decomposition rate of NA2 **1.30** was considerably slower compared with NCS-chr **1.1**. The intense DNA damage by NA2 **1.30** was noticeably observed at thymidine and adenine base sites. The prevalence of the attacked bases was very similar to NCS-chr but different from C-1027 **1.29**, esperamycin A_1 **1.3**, and calichemicin γ_1 **1.4**. Nevertheless, a more random DNA cleavage profile of NA2 **1.30** was observed when compared with NCS-chr **1.1**. Miyagawa and co-workers[49] suggested that the methylamino group of the NCS-chr **1.1** aminoglycoside moiety engages in the specific recognition of the thymine base by generating a hydrogen bond with the C2 carbonyl of the thymine base. Furthermore, the authors proposed that the naphthoate ring undergoes stacking interaction with DNA bases.

Interestingly, NA2 **1.30** can cleave DNA even in the absence of thiol agents whereas the activation of NCS-chr **1.1** relies on thiol agents such as dithiothreitol, methyl thioglycolate and glutathione.[50] Alternatively, the presence of thiol agents increases the activation of NA2 **1.30** further.[50]

1.1.1.8. *Maduropeptin*

In 1991, a complex of macromolecular antibiotics known as Maduropeptin was isolated from the broth filtrate of *Actinomadura madurae*.[51] According to reports, maduropeptin comprises of a 1:1 complex of an acidic, water soluble 32 kDa carrier protein. In addition, the maduropeptin possesses a nine-membered ring enediyne chromophore that carries remarkable antibacterial and antitumor properties (**Figure 1.2**).[52] Schroeder *et al.*[52] documented the

structure of the maduropeptin chromophore **1.31** and described the nine-membered ring diyne as the methanol adduct of a structurally unknown labile chromophore. Maduropeptin chromophore **1.31** demonstrates intense antitumor and antibacterial activities.[53] However, the mechanism which accounts for these activities differs from similar enediyne natural products.[53] The highly strained system **1.41**, cycloaromatises spontaneously to the *p*-benzyne bi-radical which can effectively cleave DNA. In conclusion, **1.31** exhibits a stable, pro-drug version of the reactive nine-membered enediyne structure. Remarkably, the total synthesis of maduropeptin has recently been accomplished by Khan *et al.*[54]



Scheme 1.4: The Mechanism of DNA Cleavage by Maduropeptin

1.1.1.9. *Uncialamycin*

Only recently, the cyclic ten-membered enediyne uncialamycin **1.32** was collected in British Columbia, isolated from the surface of lichen *Cladonia uncialis*.[55] Similar to dynemicin A **1.6**,[16,17] the structure of uncialamycin **1.32**, amalgamates a ten-membered enediyne with an anthraquinone substructure. Initial biological analyses demonstrated that **1.32** possesses potent *in vitro* antibacterial activity against to Staphylococcus aureus, Escherichia coli and Burkholderia apia.[55] Although there was a small amount of product available (~300 μg were isolated) the structure of **1.32** was resolved but attributing the absolute configuration of C26 was not possible. Recently, research by Nicolaou *et al.*[56] demonstrated unequivocal evidence for the structure of **1.32** in its entirety. Furthermore, the findings identified the absolute stereochemistry at C26 following total synthesis of the racemic mixture and reported the first asymmetric synthesis.[57] Able to access sufficient quantities of **1.32** and its C26-epimer **1.33**, Nicolaou and co-workers examined its biological properties in DNA-cleavage, antibacterial and cytotoxic activities. These studies indicated promising, high potent antitumor activities and broad-spectrum antibacterial properties.[57]

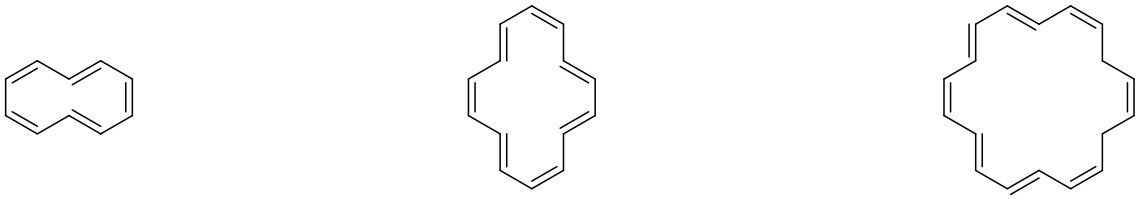
1.1.2. The Bergman Cyclisation

1.1.2.1. *Pre-Bergman Cyclisation*

1.1.2.1.1. *Work by Sondheimer*

Originally defined by Sondheimer in the early 1960s,[58] an [*n*]annulene is a monocyclic hydrocarbon comprised of alternating single and double bonds. The annulenes have been studied extensively due to their potentially aromatic character.[59] The synthesis of [6]-annulene (benzene), and [8]-annulene (cyclooctatetraene) were reported in the early 20th century.[60] The synthesis of the following compounds in the series was highly sought after, with particular interest given to the aromatic annulenes. According to Hückel's rule,[61] the following aromatic compounds of the series were the [10]-annulene and [14]-annulene, **1.45** and **1.46** respectively. However, as it was previously pointed out, these two molecules cannot be planar in view of the steric interactions of the internal hydrogen atoms in the planar

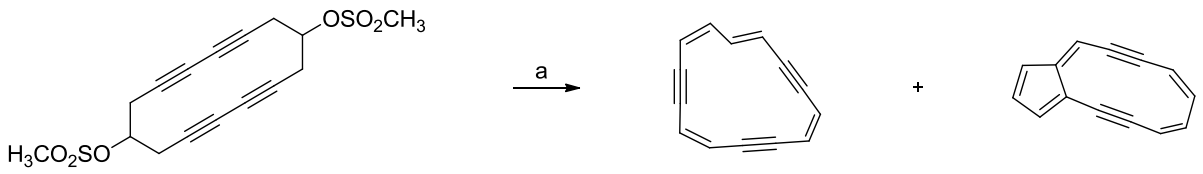
molecules. Consequently, the [18]-annulene **1.47** appeared to be the first compound of the series to be genuinely planer.



[10]-annulene **(1.45)** [14]-annulene **(1.46)** [18]-annulene **(1.47)**

Figure 1.3: [10]-, [14]- and [18]-annulenes

The major breakthrough in annulene chemistry was the synthesis of the fully conjugated macrocyclic polyenes; [18]-annulene (cyclooctadecanonaene) **1.47**, [24]-annulene (cyclotetracosadodecaene) and [30]-annulene (cyclotriacontapentadecaene) by Sondheimer *et al.*[58] This was then followed by work on the [14]-annulene **1.46** and it was intended that the [14]-annulene **1.46** could be synthesised by starting from base-induced elimination of cyclotetradeca-3,5,10,12-tetrayne-1,8-diyl dimethanesulfonate **1.48**. However, when this compound was reacted with potassium hydroxide in methanol at room temperature, extensive transannular bond formation occurred and the reaction led to the unusual bicyclic compound **1.50**.[62]

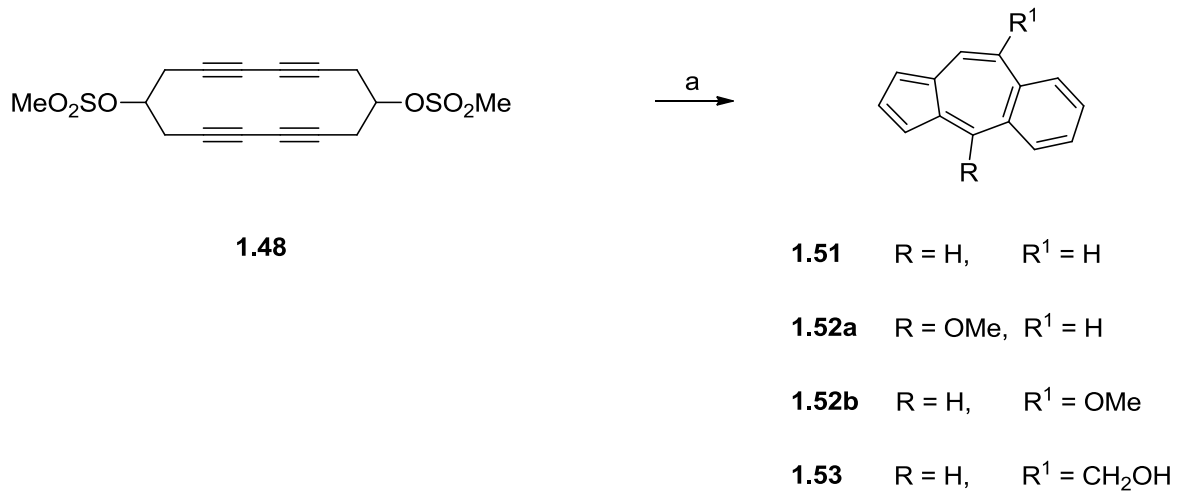


1.48 **1.49** **1.50**

Reagents and Conditions: (a) KOH, MeOH, rt, **1.49**: 1%, **1.50**: 15-20%.

Scheme 1.7: Towards the Synthesis of [14]-Annulene

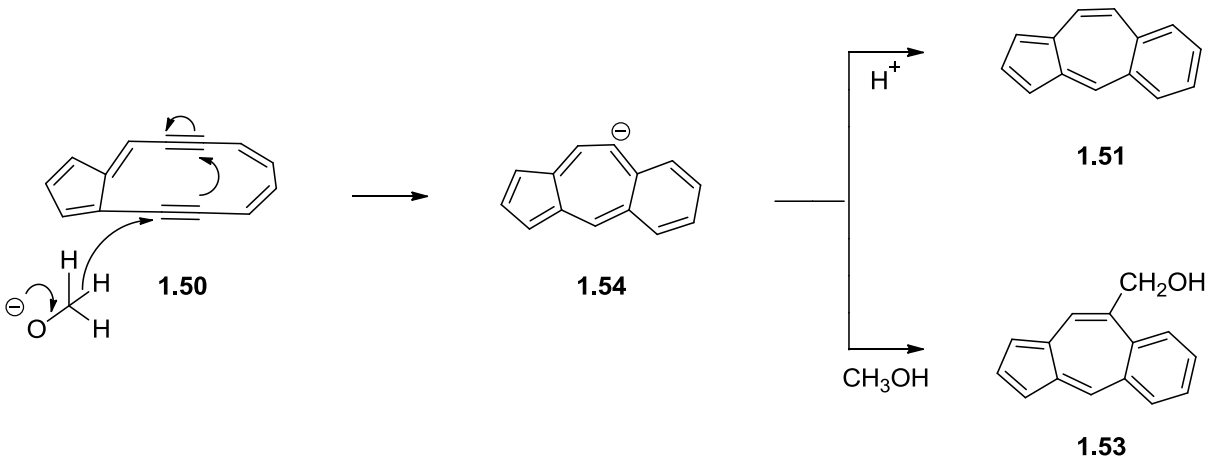
When this reaction was carried out under more vigorous conditions (**1.48** in a small volume of dimethyl sulfoxide boiled under reflux with 7% potassium hydroxide in 95% aqueous methanol for 15 min.) neither of these substances were obtained, yet the three tricyclic 5,6-benzazulene derivatives **1.51**, **1.52a-b** and **1.53** were isolated.[63]



Reagents and Conditions: (a) DMSO, 7% KOH, MeOH, H_2O, reflux, **1.51**: 25%, **1.52a-b**: 5%, **1.53**: 9%

Scheme 1.8: Cyclisation Reaction under more Vigorous Conditions

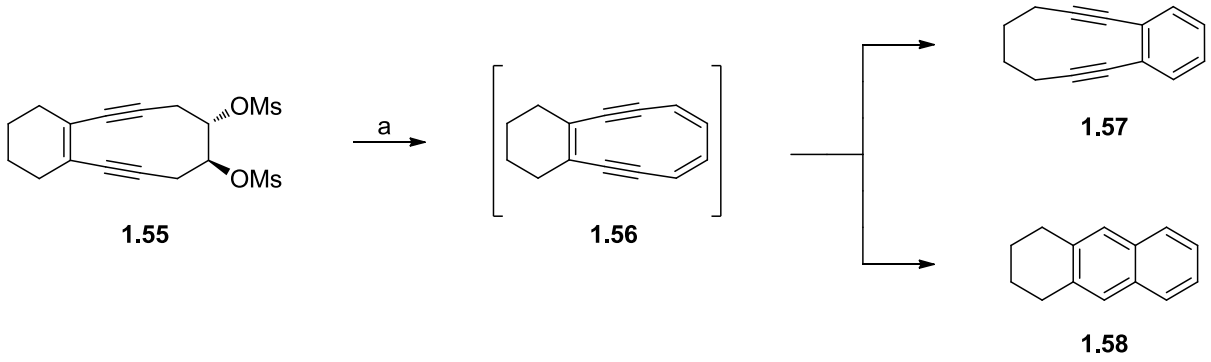
Generally, Sondheimer *et al.*[62,63] is regarded as the first group to synthesise the cyclisation product related to enediyne chemistry. The proposed mechanism of this cyclisation is that the eleven-membered ring of the bicyclic hydrocarbon **1.50** generates a fused ring-system by transferring hydride ion from methoxide under reflux. The product **1.53** is presumably formed *via* similar mechanism, the reactive intermediate **1.54** reacting with the formaldehyde prior to protonation. Similarly, the formation of compounds **152a** and **1.52b** is explained by the direct attack of methoxide onto bicyclic hydrocarbon **1.50**.



Scheme 1.9: Sondheimer's Proposed Mechanism

1.1.2.1.2. *Work by Masamune*

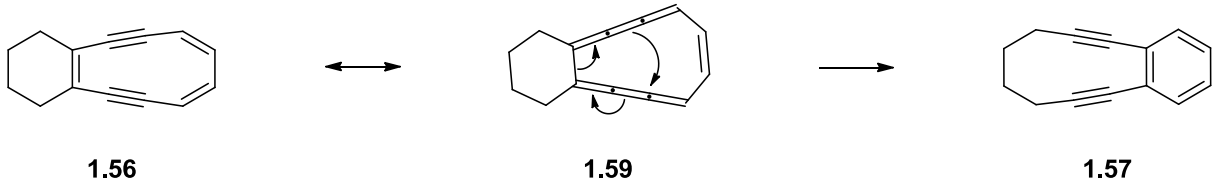
Masamune and co-workers also carried out extensive work into the formation of annulenes, particularly focusing on the synthesis of the [10]-annulene.[64,65] This organic compound is a conjugated 10-π electron cyclic system and according to Hückel's rule it should display aromaticity. However, it is not aromatic because of a combination of steric strain and angular strain. During the synthesis of [10]-annulene, Masamune and co-workers obtained surprising products which were 3,4-benzocyclodec-3-ene-1,5-diyne **1.57** and 1,2,3,4-tetrahydroanthracene **1.58** instead of the desired dehydro annulene **1.56**.



Reagents and Conditions: (a) NaOMe, MeOH.

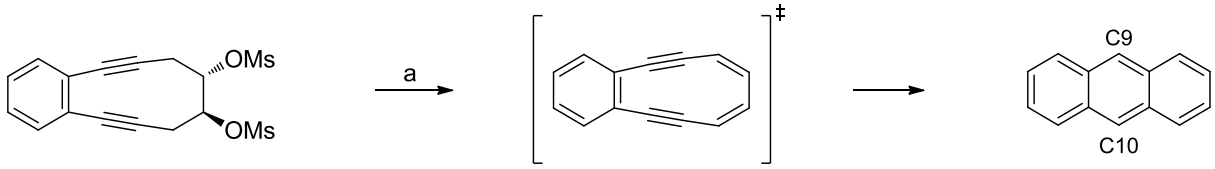
Scheme 1.10: Towards the Synthesis of [10]-Annulene

Treatment of the dimesylate **1.55** with sodium methoxide produced both the bicyclic and tricyclic compounds 3,4-benzocyclodec-3-ene-1,5-diyne **1.57** and 1,2,3,4-tetrahydro anthracene **1.58**, as shown in **Scheme 1.10**. The authors did not give a mechanism for the formation of 1,2,3,4-tetrahydroanthracene **1.58** but did give a suggested mechanism for the formation of 3,4-benzocyclodec-3-ene-1,5-diyne **1.57**. The suggested mechanism proceeds *via* a "Cope-like" rearrangement. The proposed mechanism of the formation of compound **1.57** is shown in **Scheme 1.11**.



Scheme 1.11: Masamune's Proposed Mechanism

Further studies by Masamune using an aromatic dimesylate **1.60** for the formation of 1,5-didehydro-3,4-benz[10]annulene **1.61** yielded only anthracene **1.62** (**Scheme 1.12**). Use of the deuteriated solvents in the reaction showed that the two additional hydrogen atoms were inserted at the C9 and C10 positions. No mechanism for this reaction was suggested at the time but it was suggested that 1,5-didehydro-3,4-benz[10]annulene **1.61** was formed. Subsequently, it decomposed by an unknown mechanism to form anthracene **1.62.**



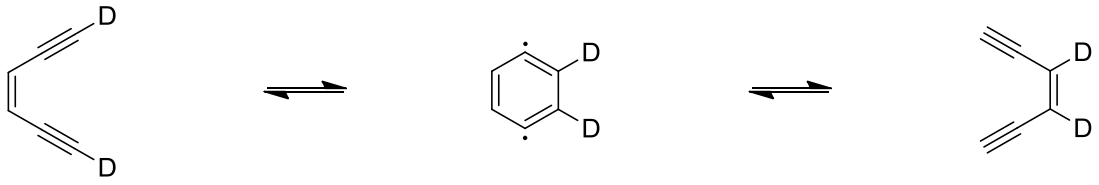
1.60 **1.61** **1.62**

Reagents and Conditions: (a) KOH, MeOH.

Scheme 1.12: Formation of Anthracene **1.62**

1.1.2.2. *Bergman Cyclisation*

In the early 1970s Bergman and co-workers postulated that upon thermolysis, the parent *cis*-hex-3-ene-1,5-diyne **1.63** containing deuterium in the acetylenic positions underwent a symmetry-allowed rearrangement to the reactive intermediate 1,4-didehydrobenzene **1.64**.[66] Subsequently, this could collapse to the starting material or the rearrangement product **1.65**.

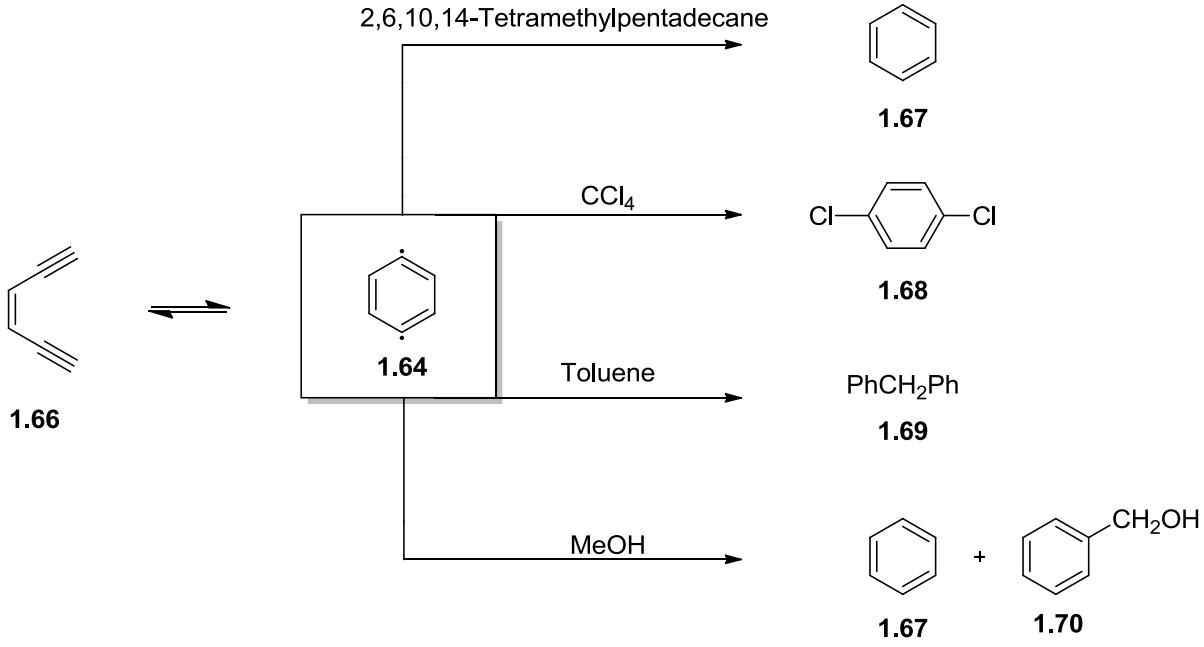


1.63 **1.64** **1.65**

Scheme 1.13: Original work by Bergman *et al.*[66]

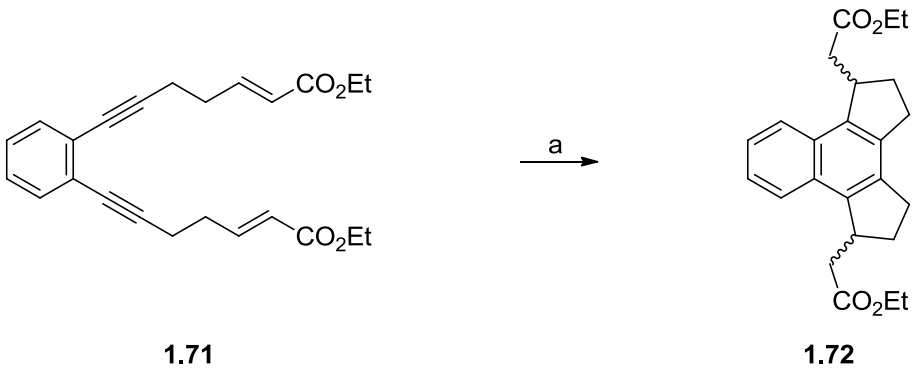
In order to trap the bi-radical species **1.64**, this reaction was performed in a range of solvents. When *cis*-1,5-hexadiyn-3-ene **1.66** was heated in 2,6,10,14-tetramethylpentadecane at 200 °C in 0.01M concentration of the starting material (to avoid polymerisation), benzene **1.67** was generated.[66,67] Likewise, 1,4-dichlorobenzene **1.68,** diphenylmethane **1.69** and benzyl alcohol

1.70 were obtained when using either CCl_4, toluene or methanol as the respective solvents.[67] All these reactions provided further evidence for the occurrence of Bergman's bi-radical intermediate **1.64**; the results are shown in **Scheme 1.14**.



Scheme 1.14: Trapping of Bi-radical

The radical nature of the intermediate was further demonstrated by Grissom and co-workers when the bi-radical, generated *in-situ* from benzodiyne **1.71**, was trapped *via* a double intramolecular 5-*exo* cyclisation onto two *α,β*-unsaturated esters (**Scheme 1.15**).[68] The bi-radical intermediate was formed using the Bergman reaction of benzodiyne **1.71** in chlorobenzene at 230 °C and with 1,4-cyclohexadiene as hydrogen atom donor.

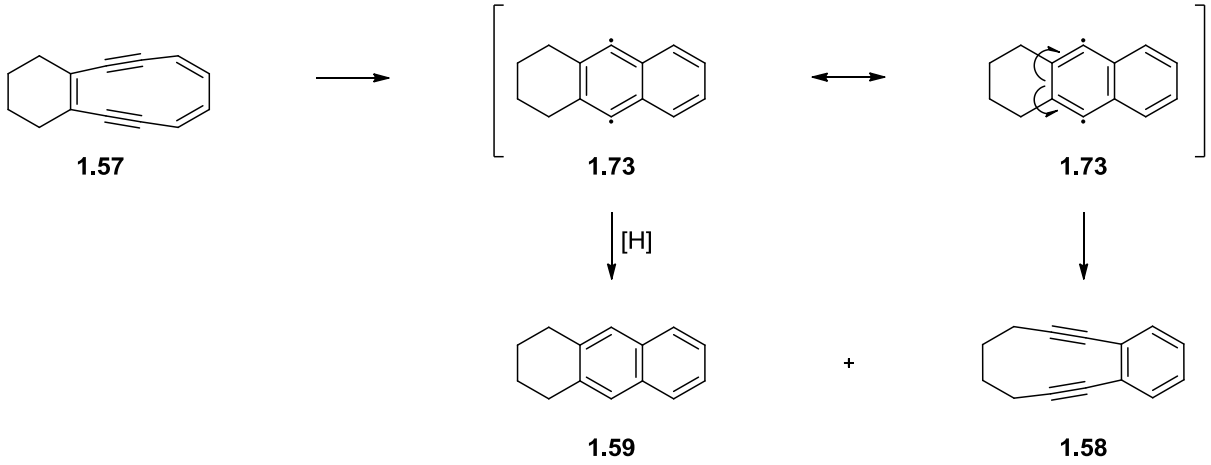


Reagents and Conditions: (a) PhCl, 1,4-cyclohexadiene, 230 °C, 6h, 99%.

Scheme 1.15: Trapping the Bi-radical

Bergman's report was the first to elucidate the details of this unusual transformation, despite its disguised appearance in the literature the previous year.

The account by Masamune *et al.*[64,65] showed the conversion of a cyclic, benzannulated enediyne to anthracene. Furthermore, Masamune's explanation incorporated two H-atoms at the 9,10-positions of the product without direct implication of the now signature 1,4-diradical intermediate.



Scheme 1.16: Masamune's Work Explained by the Bergman Reaction

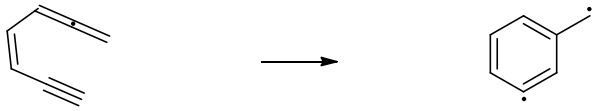
Similarly, Sondheimer's observations could also be explained by the formation of a bi-radical.[58,62,63]

Since its discovery, the Bergman cyclisation has advanced many fields of endeavour such as mechanistic organic chemistry,[69] material science[70,71] and drug discovery.[72] It has also provided a unique opportunity for testing the accuracy of computational methods.[73]

1.1.3. Myers-Saito Cyclisation

1.1.3.1. *The Chemistry of Myers et al.*

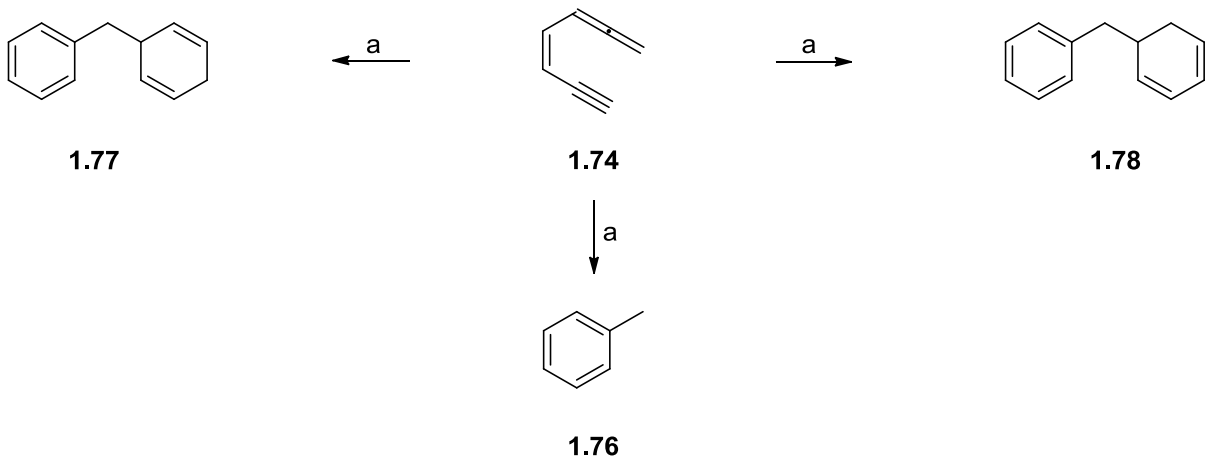
To develop the work carried out on the neocarzinostatin chromophore **1.1,** Myers *et al.*[74,75] replicated the cumulene system in an open chain as (*Z*)-1,2,4-heptatrien-6-yne **1.74**. This led to the finding that the cumulene system goes through a first-order thermal reaction to yield an intermediary α,3-dehydrotoluene bi-radical **1.75** (**Scheme 1.17**).



1.74 **1.75**

Scheme 1.17: Myers-Saito Cyclisation

Fascinated by this newly unearthed reaction, Myers and co-workers tested the thermal cyclisation on rudimentary enyne-allene system **1.74**. An intriguing reaction was detected between the acetylene and allene portions with creation of products **1.76**, **1.77** and **1.78** (**Scheme 1.18**). Their isolation was accredited to the transitional nature of bi-radical **1.75** (**Scheme 1.17**).[75,76]



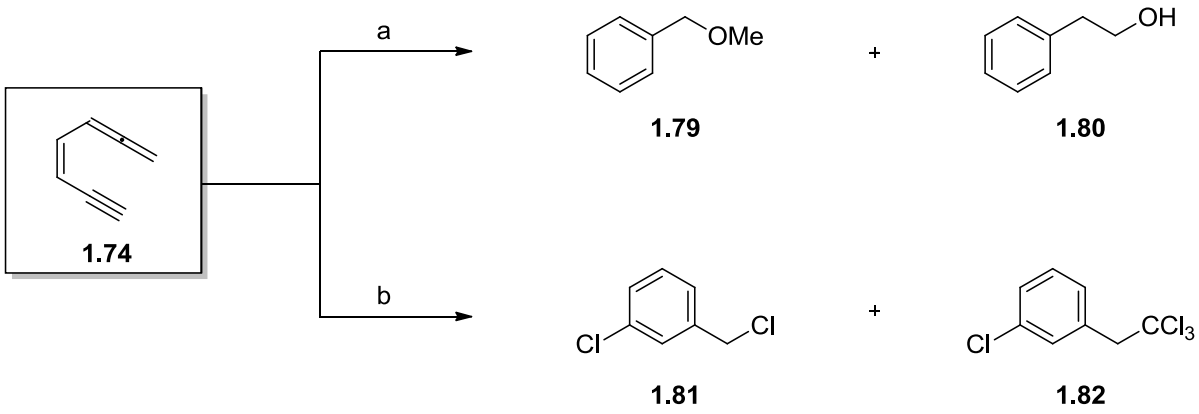
1.77 **1.74** **1.78**

1.76

Reagents and Conditions: (a) 1,4-Cyclohexadiene, reflux, 0.003M, **1.76**: 60%, **1.77**: 20%, **1.78**: 20%.

Scheme 1.18: First Reported Myers Cyclisation

In succession, the formation of a bi-radical system was evidenced by experimental work; thermolysis of **1.74** in methanol and carbon tetrachloride supplied trapped products **1.79**, **1.80**, **1.81** and **1.82** (**Scheme 1.19**).[75]

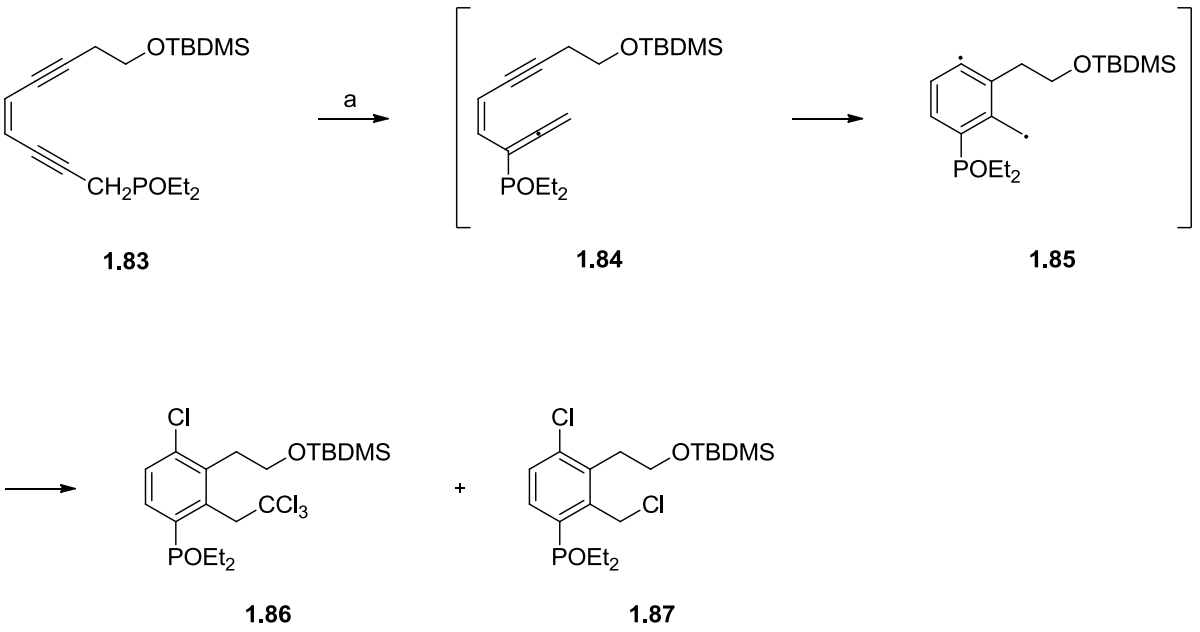


Reagent and Conditions: (a) MeOH, 0.003M, 100 °C, 30 min., **1.79**: 35%, **1.80**: 10%; (b) CCl_4, 0.003M, 100 °C, 30 min., **1.81**+**1.82**: 15-25%.

Scheme 1.19: Trapping Studies by Myers *et al.*[75]

1.1.3.2. *The Chemistry of Saito et al.*

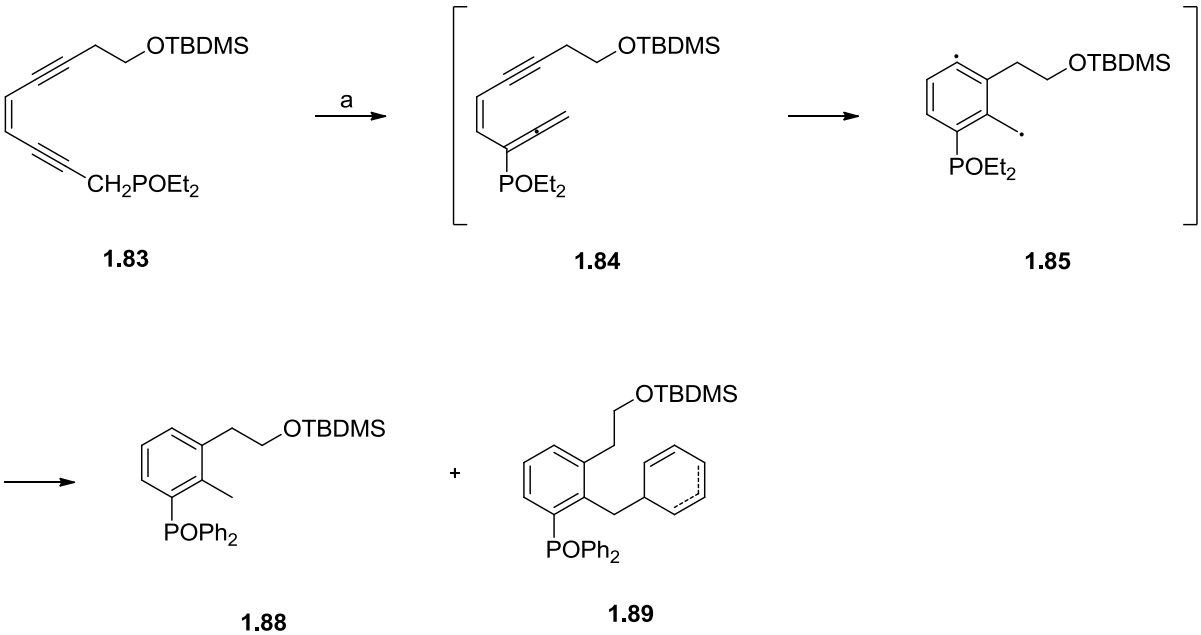
Concurrently, Saito and co-workers were investigating the Bergman cyclisation and the disparity suggested by studies of neocarzinostatin chromophore **1.1**.[77] The work of Saito and co-workers initiated with the theory that interchange of one of the alkyne groups in the Bergman cyclisation for an allene **1.84**, would significantly decrease the *cd* distance in the designed system. The formation of the desired starting material **1.84** was unsuccessful, resulting in the products **1.86** and **1.87** (**Scheme 1.20**). However, classification of the two prominent products triggered the hypothesis that the desired compound **1.84** had been formed and unexpectedly cyclised to generate the aromatic products detected.



Reagents and Conditions: (a) CCl_4, 45 °C, 1.5h.

Scheme 1.20: Reaction Development by Saito *et al.*[77]

To validate the existence of the bi-radical intermediate **1.85**, the reaction was replicated under adjusted conditions with 1,4-cyclohexadiene as a radical trap (**Scheme 1.21**).



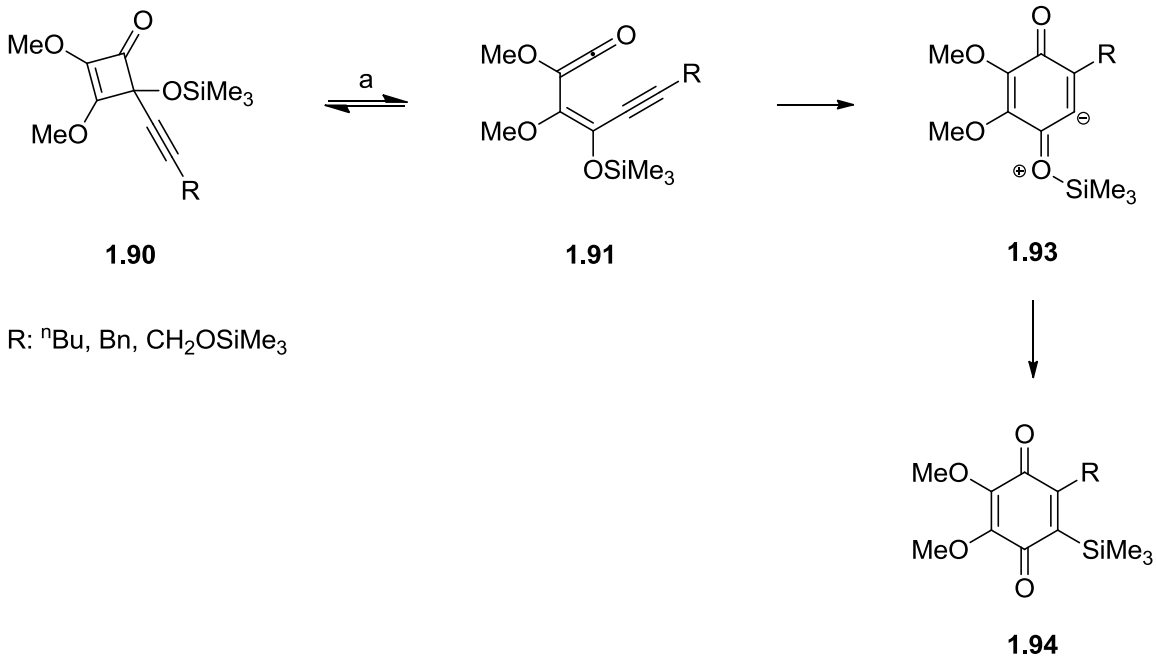
Reagents and Conditions: (a) 1,4-cyclohexadiene, 37 °C, 5h.

Scheme 1.21: Radical Quenching with 1,4-Cyclohexadiene

After five hours, the reaction furnished the cyclised products **1.88** and **1.89** by following the suggested bi-radical intermediate **1.85**, maintained by provision of hydrogen in the anticipated positions (**Scheme 1.21**).

The Myers-Saito (C^2-C^7) cyclisation of enyne-allenes has been a hot topic in recent years since α,3-didehydrotoluene bi-radicals play an important role in DNA-cleavage reactions[78] and subsequent reactions of synthetic interest.[79]

It is likely that the most comprehensively studied area of the synthetic utility of a Myers-Saito type reaction includes the use of eneyne ketenes. These have been investigated by Padwa *et al.*[80,81] and *Nakatani et al.*[82] but most prominently by Moore *et al.*[83] in a synthetic framework. The work by Moore *et al.*[83,84] included the *in-situ* generation of an eneyne ketene from a substituted cyclobutene which then underwent a reaction analogous to the Myers-Saito reaction (**Scheme 1.22**).

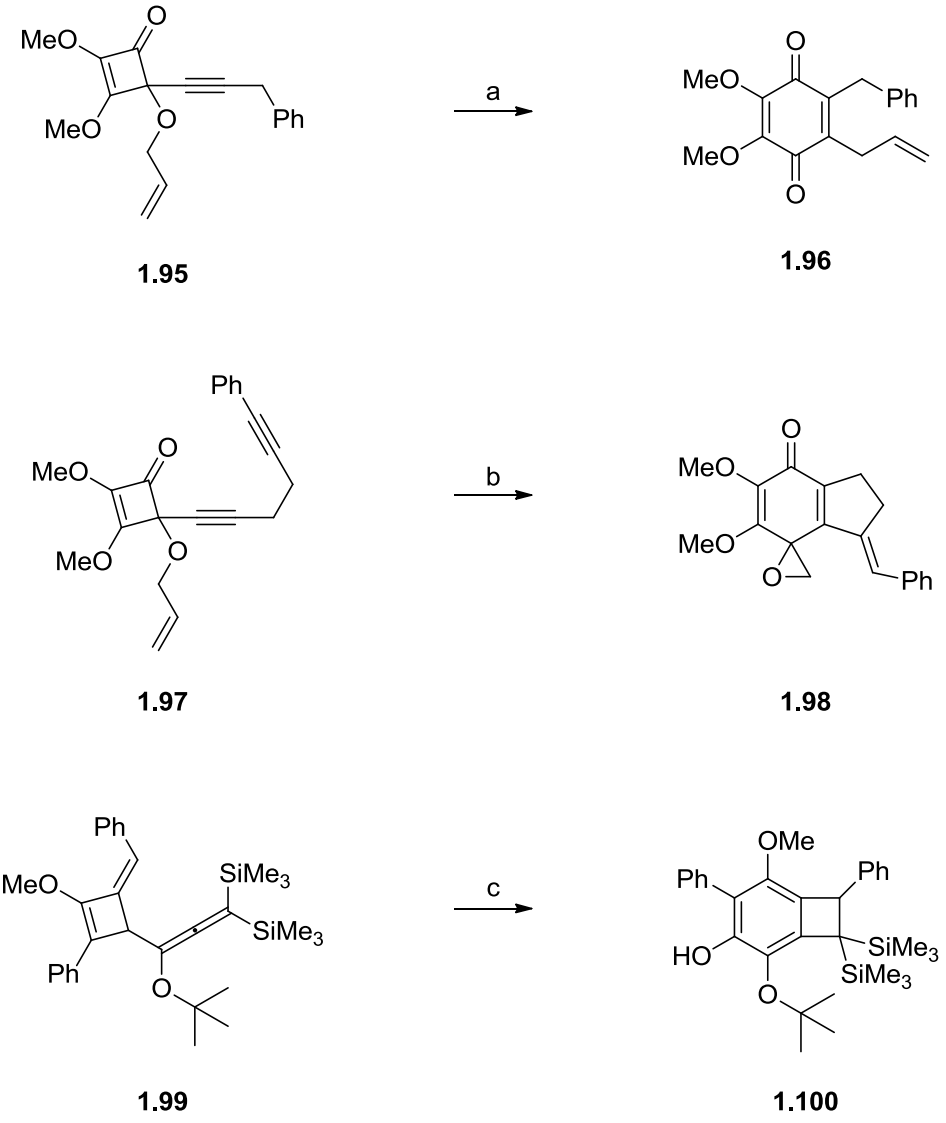


Reagents and Conditions: (a) *p*-Xylene, 135 °C, 75-80%.

Scheme 1.22: Initial Work by Moore *et al.*

In light of subsequent developmental work by Moore *et al.*[85] and the protocols for derivatisation of squaric acid derivatives in the literature,[86] the Moore reaction established a highly useful entry into the substituted quinones. Evidence of this usability can be found in

the synthesis of allylquinone **1.96**, spirocycle **1.98** and benzocyclobutene **1.100** (**Scheme 1.23**) by Moore *et al*.[85]



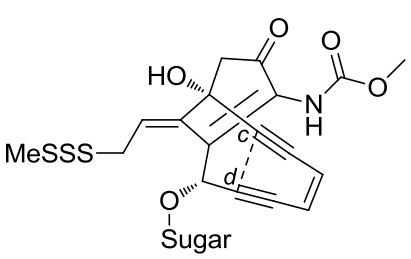
Reagents and Conditions: (a) *p*-Xylene, reflux, 76%; (b) Toluene, reflux, 91%; (c) *p*-Xylene, reflux, 49-64%.

Scheme 1.23: Examples of Moore Reactions

1.1.4. Factors Determining the Reactivity of Enediynes in the Cyclisation Processes

1.1.4.1. *Theory of Distances*

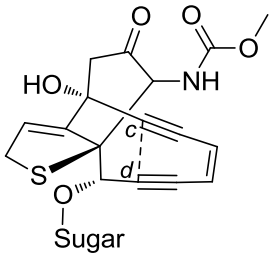
Early work on the synthesis and examination of enediyne fragments reinforced a relationship between the critical internuclear distance of the forming carbon-carbon bond and the cyclisation barrier.[87,88] The acetylenic substitution determines this distance, which can also be affected by ring size if the acetylenes are linked *via* a larger macrocycle. Nicolaou *et al.*[87] proposed that compounds with distances of less than 3.20Å should undergo spontaneous cyclisation. Alternatively, when distances were higher than 3.31Å the enediyne was relatively stable at ambient temperature. In conclusion, it was regarded that the length of 3.20-3.31Å was critical for reactivity.



cd = 3.35 Å

stable at room temperature

1.9



cd = 3.16 Å

spontaneous cyclisation

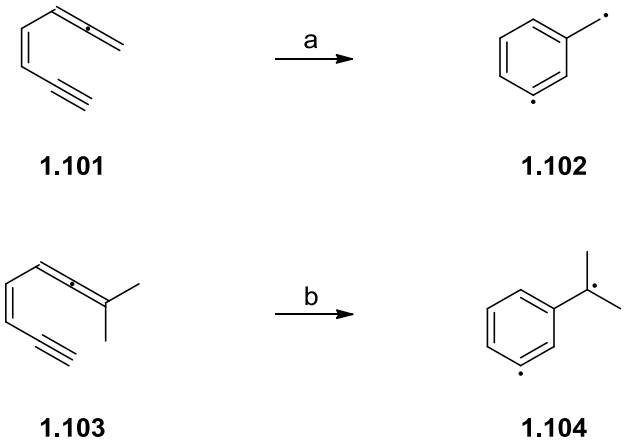
1.10

Figure 1.4: Calculated *cd* Distance: Effect on the Bergman Cyclisation.

Following the calculation of activation energies of monocyclic enediynes of varying size,[89] Schreiner proposed the extension of this critical reactivity range to encompass internuclear distances covering 2.90-3.40Å.[89] In conclusion of the enediyne reactivity analysis, Alabugin and Manoharan demonstrated that the critical distance of 3.20Å is characteristic of spontaneous cyclisation. This is explained by the attractive two-electron interaction of the in-plane π-π/ orbitals outweighing the repulsive contribution of the π-π interaction.[90]

Similar to the arrival of aromatic systems from enediynes as a result of Bergman cyclisation, (*Z*)-hepta-1,2,4-trien-6-ynes are able to yield cyclised systems *via* α,3-didehydrotoluene diradicals. In contrast to Bergman cyclisation, acyclic enyne-allenes **1.101** and **1.103** react in accordance to Myers-Saito at ambient temperatures.[91,92] Furthermore, the reaction of cyclic

enyne-allenes is similar to acyclic analogues and neocarzinostatin demonstrates biological activity through the instigation of such reaction.[93]



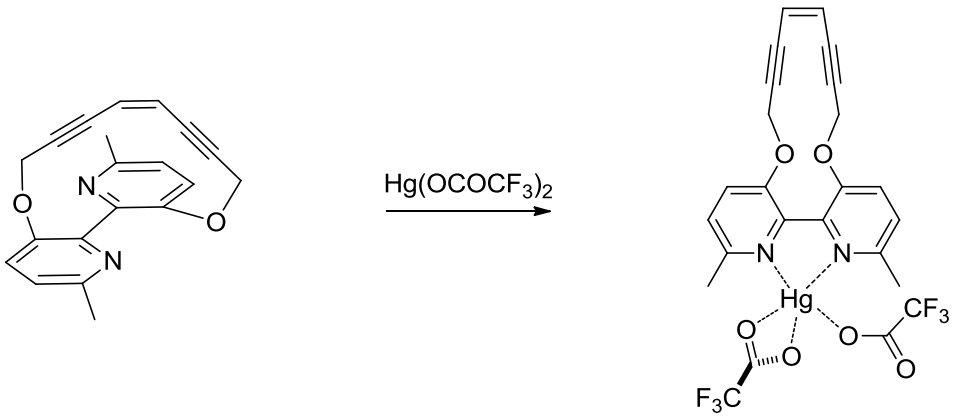
1.101 **1.102**

1.103 **1.104**

Reagents and Conditions: (a) 24h, 37 °C or 30 min., 75 °C; (b) 70 min., 37 °C.

Scheme 1.24: Myers-Saito Cyclisation

Furthermore, metal coordination has been demonstrated as a potentially useful approach for enabling Bergman cyclisations under reasonably mild conditions. [94]



1.105 **1.106**

Scheme 1.25: Decreasing the *cd* Distance with Metal Coordination

In the absence of metal-ion complexation, the bipyridyl unit in **1.105** occurs in the transoid conformation which drives the terminal acetylenic carbon atoms to be far apart. Once metal-ion binding takes place, the 2,2'-bipyridyl unit alters into a cisoid conformation that allows the bidentate ligands to coordinate to the metal ion. During the process, the *cd* distance

decreases and an increase in thermal reactivity is expected, this was indeed the case. The thermal stability of compound **1.105** and its Hg^{2+} complex **1.106** exhibited significant difference. Although a temperature of approximately 237 °C is required to induce irreversible thermal cyclisation of **1.105**, the Hg^{2+} complex **1.106** reacts at approximately 145 °C.

Furthermore, there have been fewer studies carried out on derivatives with increased cyclisation barriers; the large activation energy necessary for even unconstrained enediynes[95] may account for this. For example, the presence of the two propyl groups on enediyne **1.108** significantly increases the temperature necessary for cyclisation relative to **1.107**. To date, one of the most impeded systems investigated is (*Z*)-1,6-diphenylhex-3-ene-1,5-diyne **1.109** which reacts at 280 °C.[96]

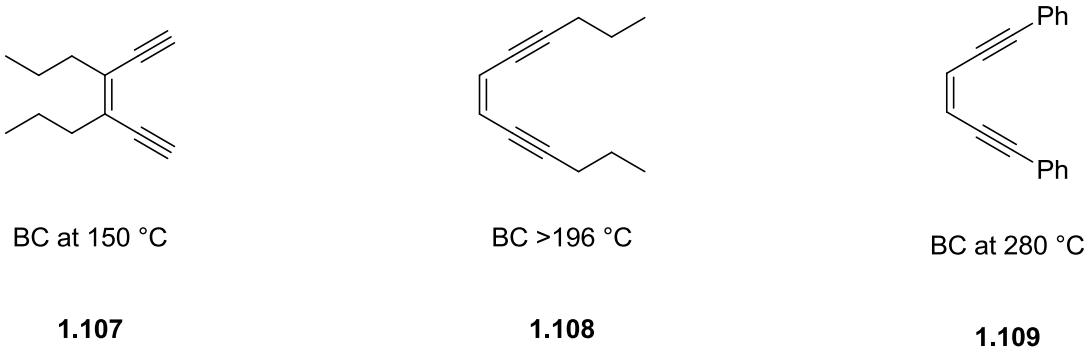
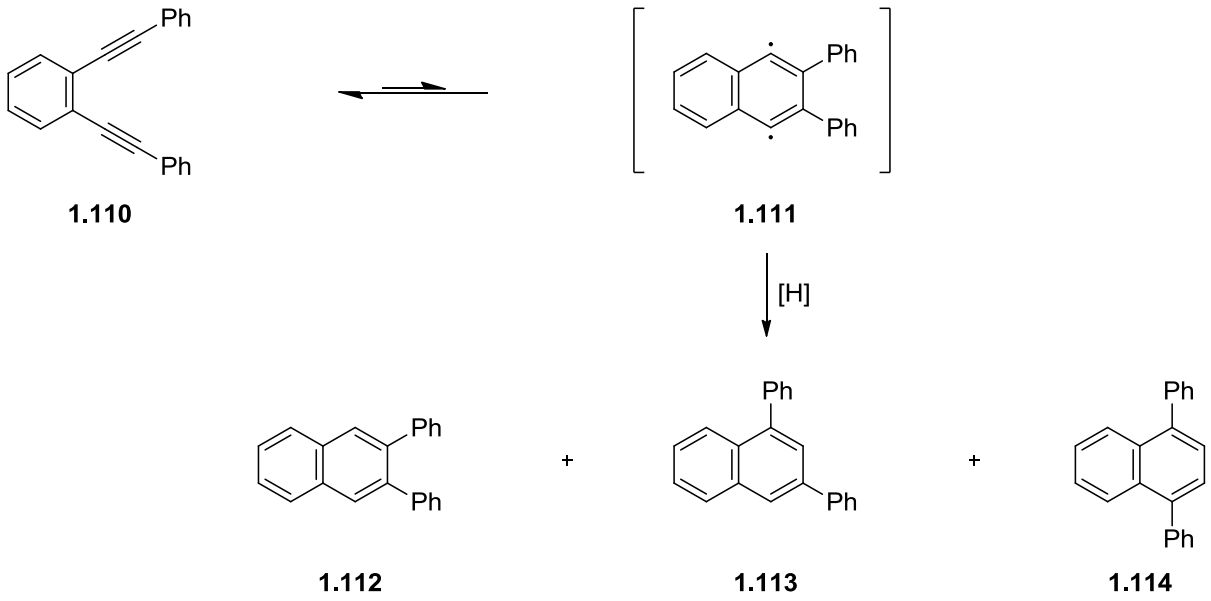


Figure 1.5: Examples of Enediyens that Undergo the Bergman Cyclisation

Unexpectedly, Lewis *et al.*[97] discovered that specific enediynes induce products that are not simply the results of cycloaromatisation but most probably derive from an initially formed 1,4-didehydroarene and involve one or more phenyl shifts. An example of this can be found in the reaction of 1,2-bis(phenylethynyl)benzene **1.110**, which yielded the expected isomer 2,3-diphenylnaphthalene **1.112** as a minor product (<3% yield) under all conditions studied.[97] The dominant species formed were 1,3-diphenylnaphthalene **1.113** (16%) and 1,4-diphenylnaphthalene **1.114** (11%), resulting from single and double phenyl shifts, accordingly.

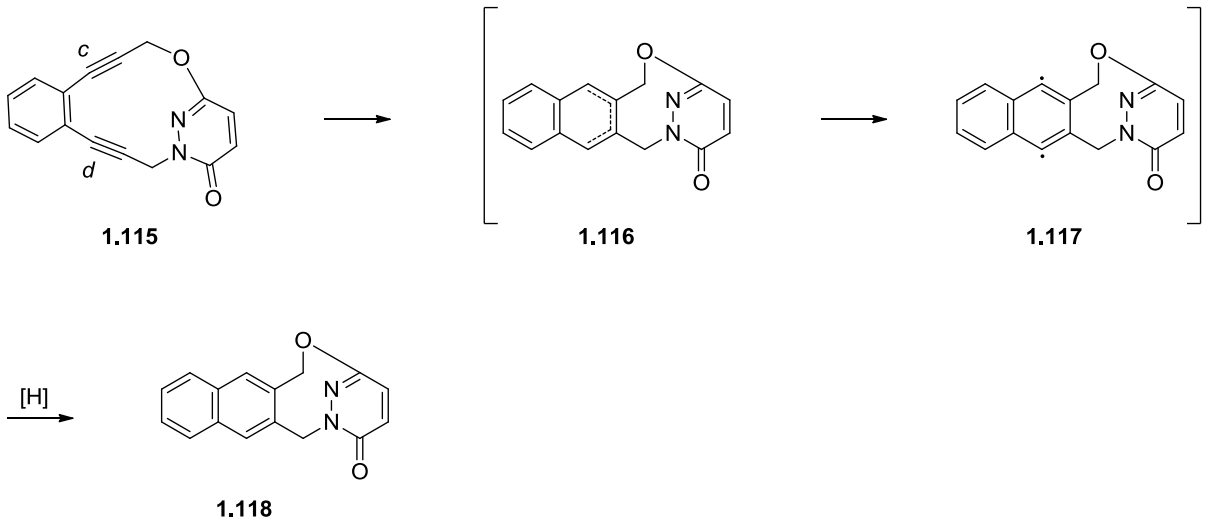


Scheme 1.26: Reaction of Diphenyl-Substituted Diethynylbenzene and Observed Phenyl-Shifted Products

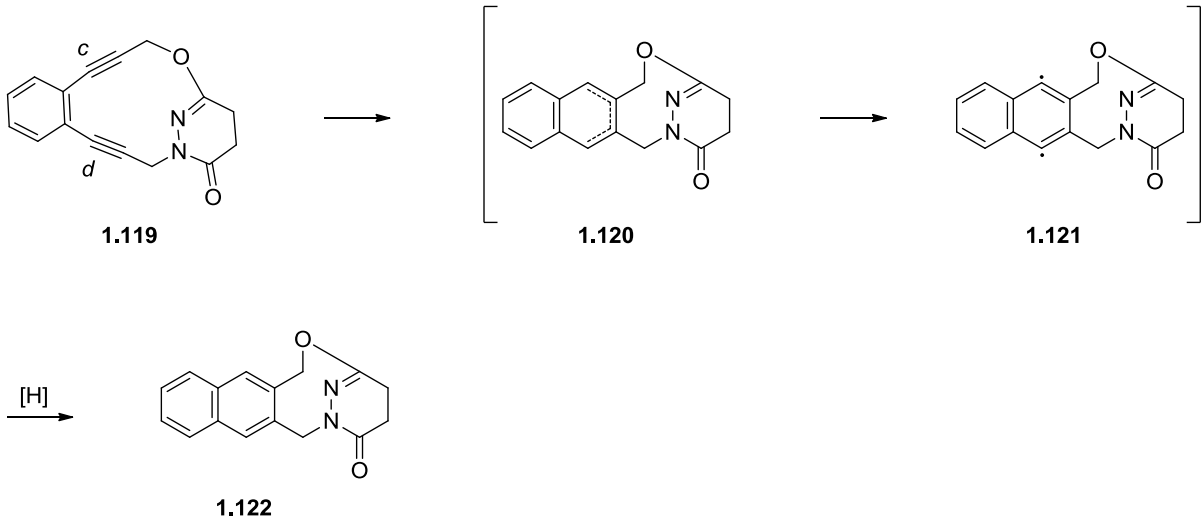
1.1.4.2. *Effect of Strain* in the Chromophore of Cyclic Enediyne

The increase in the number of species characterised, prompted the task of finding an adequate explanation for the lowering of the cyclisation activation barrier.[98] This resulted in the proponent theory of strain release across the reaction coordinate. It was proposed that difference in molecular strains between the ground and transition states serves as the mainspring for cyclisation.[99,100] Furthermore, the use of fused ring systems, decreasing the ring strain in moving from the reactant to product became just as significant a factor in rationalising lower activation barriers.[101]

Basak *et al.*[102] presented the outcome of a distant double bond in a pyridazine system assimilated into the enediyne ring on the kinetics of Bergman cyclisation. Basak and co-workers discovered that saturation of the distant double bond quickens the process of cycloaromatisation and impacts on the instigating mechanism of this reaction. For this reason, 14-oxa-1,19-diazatricyclo[13.3.1.0]nonadeca-5(10)6,8,15(19),16-pentaene-3,11-diyn-18-one **1.115** and its dihydro analogue, 14-oxa-1,19-diazatricyclo[13.3.1.0]nonadeca-5(10),6,8,15 (19)-tetraene-3,11-diyn-18-one **1.119** were synthesised and their capacity to go through cycloaromatisation in the solid phase was examined.



Scheme 1.27: Cycloaromatisation of Compound **1.115**

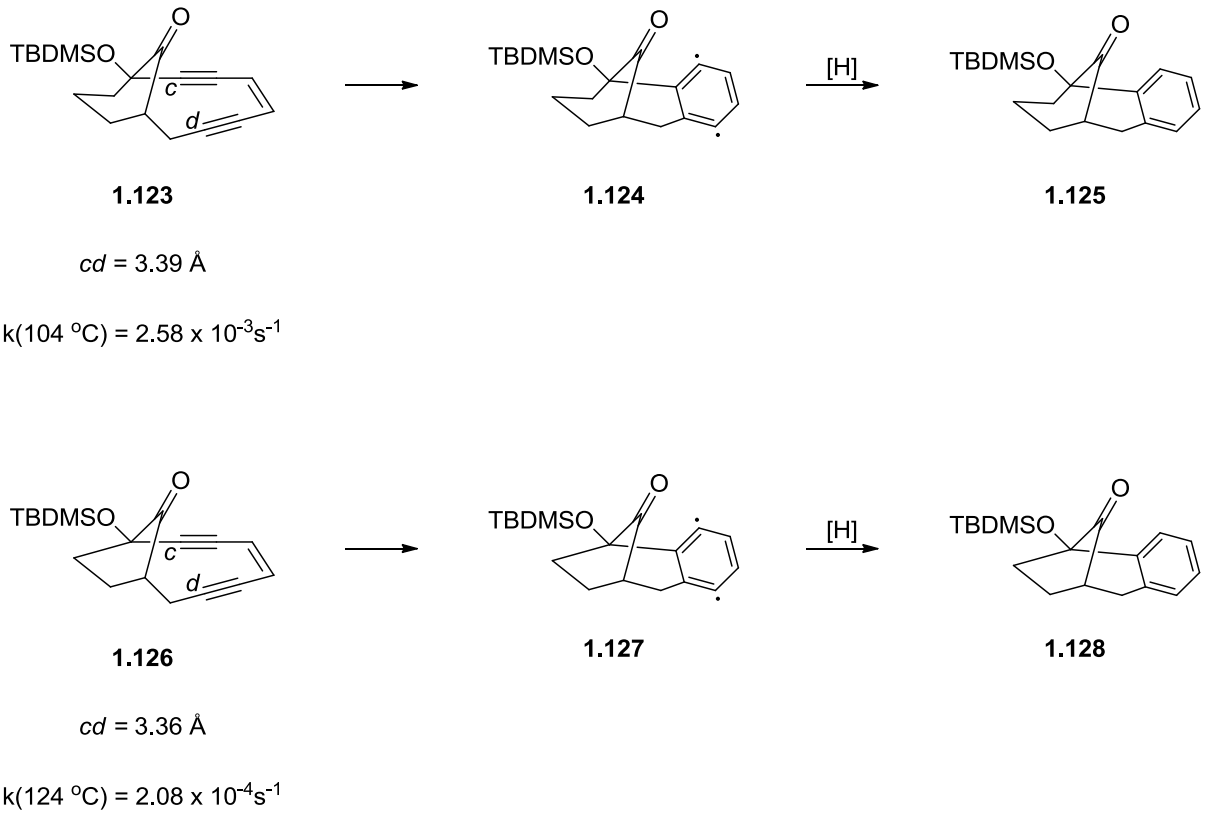


Scheme 1.28: Cycloaromatisation of Compound **1.119**

The previously mentioned solid-phase reaction was observed by differential scanning calorimetry. Both enediynes exhibited an intense exothermic peak at 228 °C and 196 °C for compounds **1.115** and **1.119**, correspondingly. Although the *cd* distances in the molecules of both enediynes are equivalent (3.79Å), saturation of the C4=C5 bond in the heteroring alters the activation barrier to Bergman cyclisation. These findings signify a significantly higher reactivity of enediyne **1.119** in comparison to **1.115** and reveal the value of hybridization of carbon atoms in the heterocyclic chromophore.

Work by Magnus and Snyder also showed that the cycloaromatisation was not always due to a short *cd* distance.[103] Compounds **1.123** and **1.126** were synthesised and X-ray analysis of

compounds **1.123** and **1.126** showed that the *cd* distance of bicycle[7.2.1]-enediyne **1.126** was shorter than that of compound **1.123**. However, although enediyne **1.126** had the shortest *cd* distance, its cycloaromatisation reaction proved to be the most difficult (see rate constants on **Scheme 1.29**).



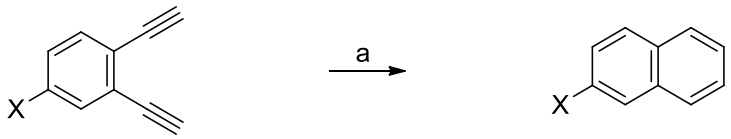
Scheme 1.29: Rate of Cyclisation of Bicylo[7.3.1] and [7.2.1]-Enediynes

In a series of photochemically activated molecules, increased reactivity for designed enediynes with high strain was noted.[104] In this particular research, the internuclear distance spanned from 3.89-4.94Å. In contrast to the critical distance hypothesis, the per cent conversion at the longest distance was 100%, while at the shortest was only 66%. Undoubtedly, both strain release and the distance between cycloaromatising carbons play a part in influencing the reactivity of enediynes.

1.1.4.3. *Effect of Electronic Factors*

Kim and Russell developed a program for studying the effects of aromaticity and electronic factors on the rate of cycloaromatisation and showed that the distance between the acetylenic

branches (*cd*), the strain energy of cyclic enediynes and electronic factors considerably affect the formation of diradicals.[105] Systematic studies on 1,2-dialkynylbenzenes **1.129a-f** revealed a linear free energy relationship between the Bergman cyclisation rate and the Hammett δ_m substituent coefficient (**Table 1.3**).[106]



1.129a-f **1.130a-f**

X = H (a), Me_2N (b), MeCO (c), MeOCO (d), CN (e),O_2N (f).

Reagents and Conditions: (a) PhCl, 1,4-cyclohexadiene. 170 °C, yields, see **Table 1.3**.

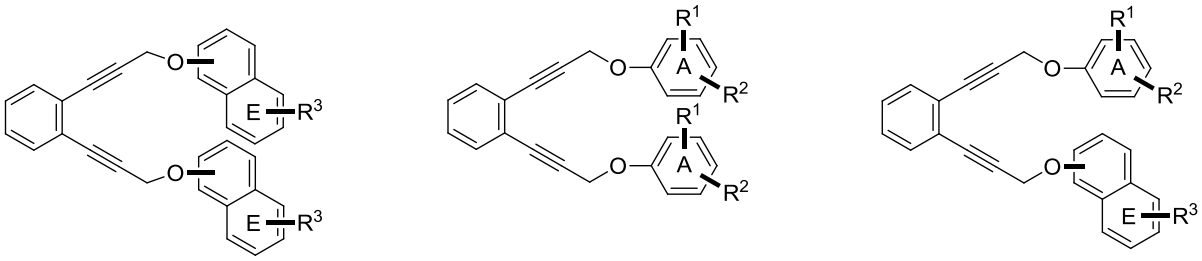
Scheme 1.30: Thermolysis of Enediynes **1.129a-f**

Compound	k x 10^{-2}, s^{-1}	$J_{1/2}$, min	Yield (%)
1.129a	2.54	11.8	-
1.129b	1.93	15.6	63
1.129c	4.66	6.5	65
1.129d	5.08	5.9	78
1.129e	5.78	5.2	60
1.129f	7.03	4.3	59

Table 1.3: Kinetic Parameters of the Bergman Cyclisations of Compounds **1.129a-f**

Weak interactions induce appreciable change in the activation profile of well-known medically important enediynes.[107] Strong electron-withdrawing groups increase the barrier to Bergman cyclisation,[108] while δ-donor groups reduce its height. The effect of π-conjugation is weak. Alabugin *et al.*[109] estimated stereoelectronic effects in cyclohexane-, 1,3-dioxane-, 1,3-oxathiane- and 1,3-dithiane-substituted enediynes. Rawat and Zaleski demonstrated steric effect of functional groups in terminal acyclic enediynes on their cycloaromatisation according to Bergman cyclisation.[110] Basak *et al.*[111] were the first to report on the synthesis

and donor-acceptor properties of a series of 1,2-dialkynylbenzenes **1.131-1.133** and on the effect of charge transfer and π-π interactions on the kinetics of Bergman cyclisation.



1.131 **1.132** **1.133**

R^1, R^2 = H, 2-NO_2, 4-NO_2, 4-CN, 3-CF_3, R^3 = H, 4-OMe

Scheme 1.31: Series of 1,2-Dialkynylbenzenes **1.131-1.133** Synthesised by Basak *et al.*[111]

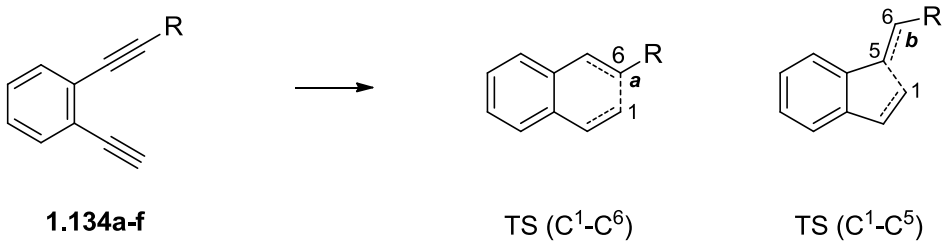
Using differential scanning calorimetry, the thermal reactivity of donor-acceptor and donor-donor pairs was shown to be higher than that of acceptor-acceptor couples.[111] The difference was attributed to intramolecular charge transfer and π-stacking between the two branches, which shorten the *cd* distance.

Additionally, stabilisation of either the enediyne or the bi-radical by conjugation and/or substitution by heteroatoms can play a role.[112]

1.1.5. Thermal C^1-C^5 Diradical Cyclisation of Enediynes

Schreiner *et al.*[113] employed computational studies for the parent enediyne **1.134a**, which demonstrated a significantly higher barrier for the C^1-C^5 diradical cyclisation than for the C^1-C^6 pathway. Nevertheless, this partiality can be reversed and the thermal C^1-C^5 diradical cyclisation is a significant and sometimes primary reaction in diaryl-substituted enediynes.

In sterically challenging systems, theoretical calculations suggest that the difference in energy between five- and six-membered ring formation is considerably reduced.[113] To assess the feasibility of C^1-C^5 cyclisation, Pascal *et al.*[114] computationally screened a number of benzannulated enediynes substituted with an aryl group at one alkyne terminus; the results are displayed in **Table 1.4**.



Scheme 1.32: Thermolysis of Enediynes **1.134a-f**

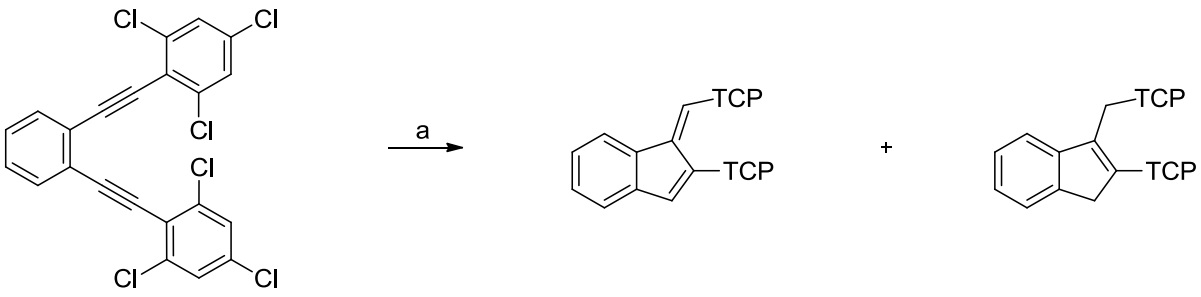
Entry	Compound	R	E_a (C^1-C^6)	E_a (C^1-C^5)
1	**1.134a**	H	24.6	37.2
2	**1.134b**	phenyl	28.7	31.4
3	**1.134c**	2,6-dichlorophenyl	30.8	31.6
4	**1.134d**	2,6-dichloro-4-nitrophenyl	31.8	31.6
5	**1.134e**	2,6-dichloro-4-aminophenyl	30.7	30.4
6	**1.134f**	2,6-dimethylphenyl	30.5	30.9

Table 1.4: Activation Energies (kcal/mol) for the Cyclisations of Monosubstituted 1,2-Diethynylbenzenes

The examination of entries 1 and 2 indicates that the activation energy for Bergman cyclisation increases by 4 kcal/mol when the hydrogen atom is replaced by a phenyl group (likely a steric effect). However, this is not the case for the C^1-C^5 pathway which decreases by 6 kcal/mol; this effect is explained by stabilisation of the emerging vinyl radical centre in the C^1-C^5 pathway and is apparent in the short phenyl-C6 bond (bond *b*) in the transition state. These particular effects do not occur in the Bergman pathway but the C^1-C^6 cyclisation maintains strong partiality for **1.134b**. Nonetheless, when a 2,6-dichlorophenyl group is substituted for phenyl (**1.134c**), increased steric effects continue to slow the Bergman reaction and the contending transition states' are brought to within 1 kcal/mol. The addition of either a nitro (**1.134d**) or an amino group (**1.134e**) to the aryl ring causes the activation energies of the C^1-C^6 and C^1-C^5 cyclisations to equalise at this level of theory.

Remarkably, thermolysis of **1.135** in toluene at 260 °C in the presence of 1,4-cyclohexadiene gave indene derivatives **1.136** and **1.137** (**Scheme 1.33**) in 19% and 50% isolated yield, accordingly. The observed products **1.136** and **1.137** reportedly arise from the C^1-C^5

cyclisation of enediyne **1.135**. Intriguingly, no Bergman cyclisation product was observed in these reaction mixtures.



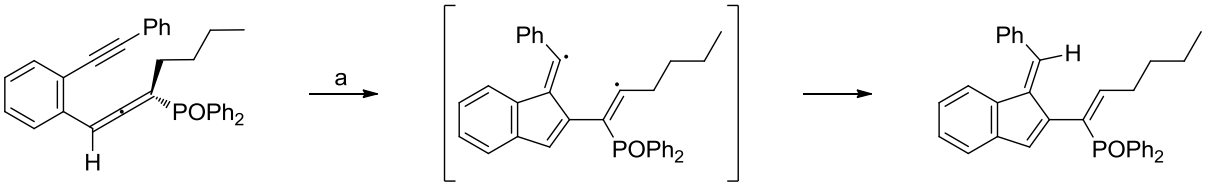
1.135 **1.136** **1.137**

Reagents and Conditions: (a) Toluene, 260 °C, 1,4-cyclohexadiene, **1.136**: 19%, **1.137**: 50%.

Scheme 1.33: Thermolysis of Enediyne **1.135**

1.1.6. The Schmittel Reaction

Whilst carrying out an investigation into increasing the activation energy of the Myers-Saito reaction, Schmittel discovered a novel reaction route. This led to an alternative bi-radical intermediate **1.139** to that reported by Myers and Saito.[115] As a consequence of the introduction of bulky groups onto the allene and alkyne units, Schmittel was aiming to cultivate a more stable allene intermediate **1.138** that would advance the investigation into the Myers-Saito.[116] On the contrary, Schmittel reported a 63% yield of product **1.140** formed *via* a C^2-C^6 cyclisation over the Myers-Saito (C^2-C^7).

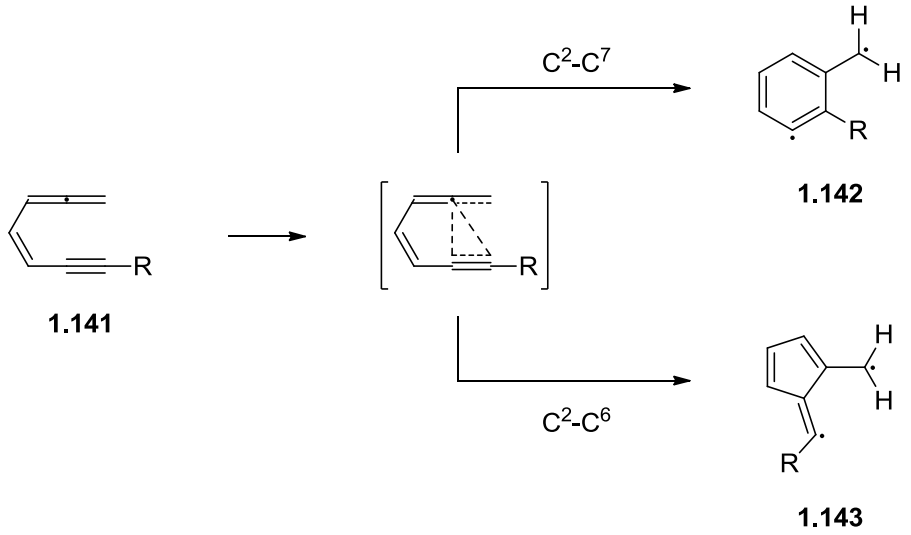


1.138 **1.139** **1.140**

Reagents and Conditions: (a) 1,4-cyclohexadiene (excess), benzene, reflux, 63%.

Scheme 1.34: Thermolysis of Enyne-Allene **1.138**

Investigations which employ experimental and computational mechanistic methods indicated that these transformations progress *via* diradical intermediates.[117] The enyne-allene systems (**Scheme 1.35**) have been accounted for by two alternative cyclisation paths: C^2-C^7 and C^2-C^6 cyclisations.

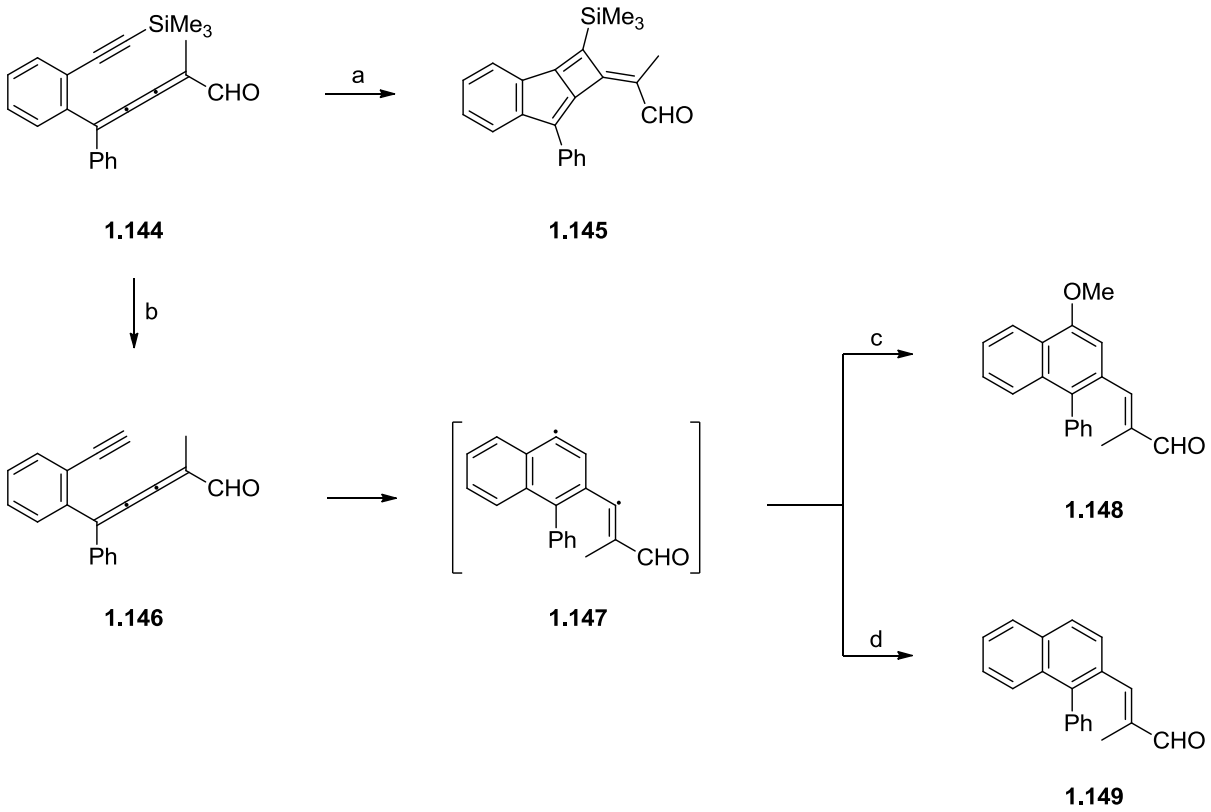


Scheme 1.35: The Myers-Saito and the Schmittel Cyclisations

For the enyne-allene system, the formation of aromaticity is the mainspring for the Myers-Saito (C^2-C^7) cyclisation. The Schmittel (C^2-C^6) route is also energetically preferred in account of the carbon hybridization conversion from sp to sp^2. Nevertheless, the C^2-C^7 cyclisation is normally favoured and relevant substitutions on alkyne termini are commonly required for adjusting the regioselectivity to C^2-C^6 cyclisation. However, the capability to construct a 5-membered ring secures the Schmittel cyclisation as an original strategy for complex poly aromatic structure construction.

A system which would select Schmittel's (C^2-C^6) cyclisation over Myers-Saito (C^2-C^7) was opportunely developed by Rodriguez.[118] More specifically, the steric hindrance supplied by a trimethylsilyl group on alkyne **1.144** favoured Schmittel's C^2-C^6 cyclisation to yield tricycle **1.145**. However, at the withdrawal of the TMS group to yield the terminal alkyne **1.146**, Myers-Saito C^2-C^7 cyclisation was favoured to give **1.148** and **1.149** as visualised by Schmittel. Respectively, the more hindered trimethylsilyl protected alkyne depended on a higher reaction temperature for the cyclisation to actualise.

Also, the regioselectivity of the cyclisation is used in the synthesis of the kinamycin[119] and the neocryptolepine[120] families in addition to the preparation of large hydrocarbons.[121] Furthermore, it becomes relevant in studying the DNA cleavage.[122]

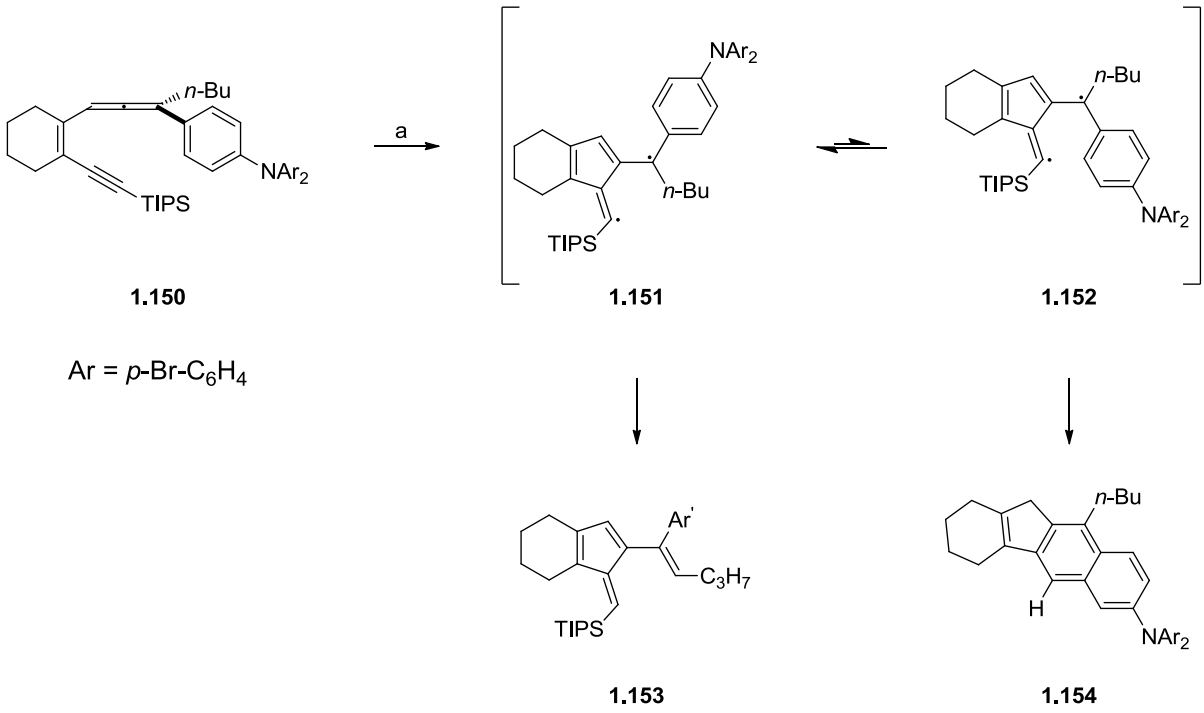


Reagents and Conditions: (a) Toluene, 110 °C; (b) K_2CO_3, MeOH; (c) Toluene, MeOH, 70 °C; (d) Toluene, 1,4-cyclohexadiene, 70 °C.

Scheme 1.36: Mode Change due to Sterics

Photochemical analogues of the Bergman cyclisation of acyclic [123,124] and cyclic[125] enediynes, as well as of natural antibiotic Dynemicin A[126] and other photochemically activated enediyne processes have spurred a number of research studies, in account of their potential application to photodynamic therapy (PDT).[127] On the contrary, photochemical analogues of the Myers-Saito or the C^2-C^6 cyclisation of enyne-allenes have endured obscurity.

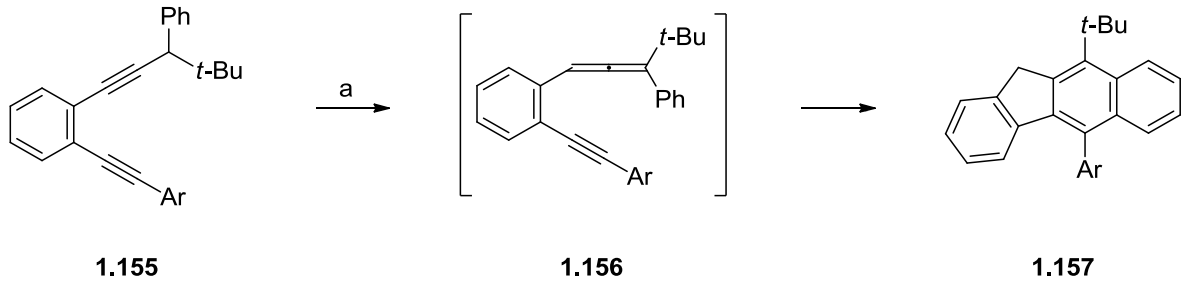
Schmittel disclosed photochemical reactions of enyne-heteroallenes,[128] these cyclisations emerged very effectively along the C^2-C^6 but intriguingly, not *via* the C^2-C^7 (Myers-Saito) pathway. Subsequent theoretical studies by Engels accounted for the preference for the C^2-C^6 route, illustrating that the process is triggered by triplet sensitisation.[129] Furthermore, for a photochemical enyne-allene cyclisation to be effective, the study advised the avoidance of benzannulated derivatives as a result of their high excitation energy. Schimittel *et al.*[130] demonstrated that photochemical C^2-C^7 and C^2-C^6 cyclisations of enyne-allenes can be activated when specially designed systems are employed.



Reagents and Conditions: (a) Toluene, *hv*, 1,4-cyclohexadiene, **1.153**: 15%, **1.154**: 15%.

Scheme 1.37: Enyne-Allene Cascade Cyclisation (Photo condition reported by Schmittel)

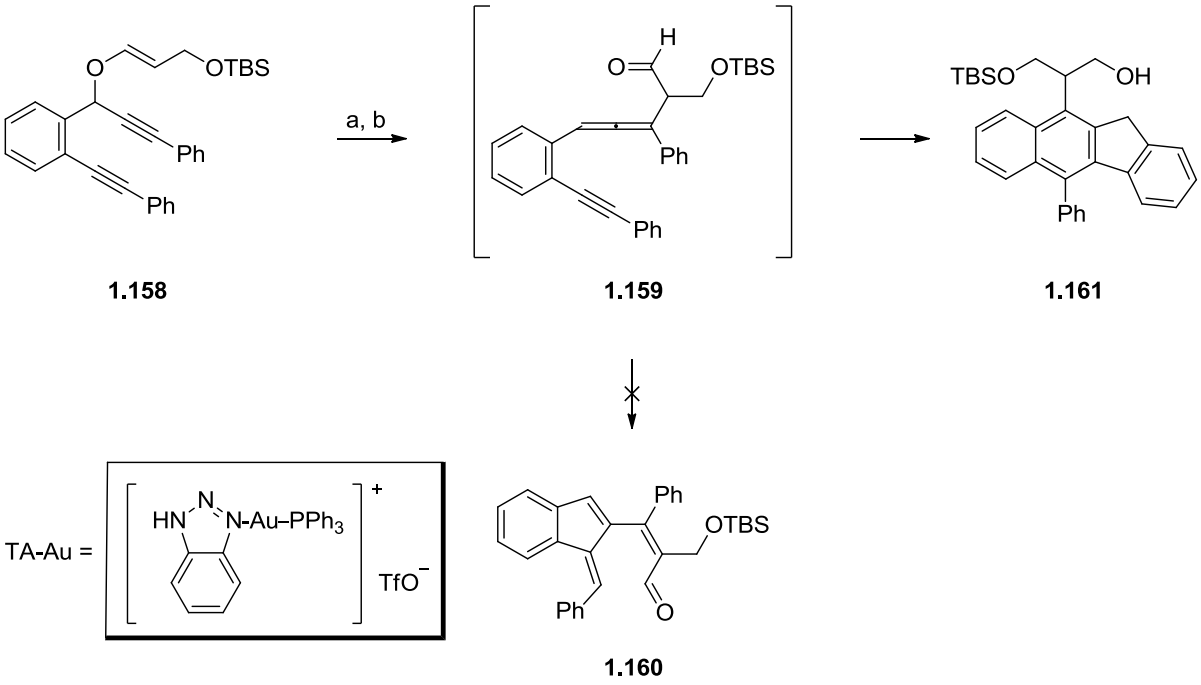
The cyclisation products **1.153** and **1.154** were produced in relatively small yields (15%) with limited selectivity (1:1). It was predicted that the diradical conformers **1.151** and **1.152** were in equilibrium. To acquire the sequential cyclisation product **1.154**, Wang suggested a different thermal strategy which utilised a bulky *tert*-butyl group to drive the diradical equilibrium towards the **1.152** conformer.[131] Compound **1.157** was then effectively acquired with improved yields. Following this, Wang *et al.*[132] demonstrated the synthetic utility of this method for the foundation of heteroaromatic and polyaromatic structures.



Reagents and Conditions: (a) Toluene, KO-*t*-Bu, reflux, 12h, 90%.

Scheme 1.38: Enyne-Allene Cascade Cyclisation (Thermal condition reported by Wang[132])

Although the C^2-C^6 cyclisation was mechanistically intriguing and synthetically encouraging, there were limitations. To begin with, the reaction conditions demanded high temperature and the total efficiency was low. Following this, the sterically hindered group was needed to drive the equilibrium to conformer **1.152** for successful aromatic cyclisation, hence limiting the reaction capacity. Recently, Wang *et al.*[133] disclosed the triazole-gold (TA-Au, 3 mol%) catalysed propargyl vinyl ether cascade rearrangement and cyclisation, to produce the preferred benzannulated indenes at room temperature.

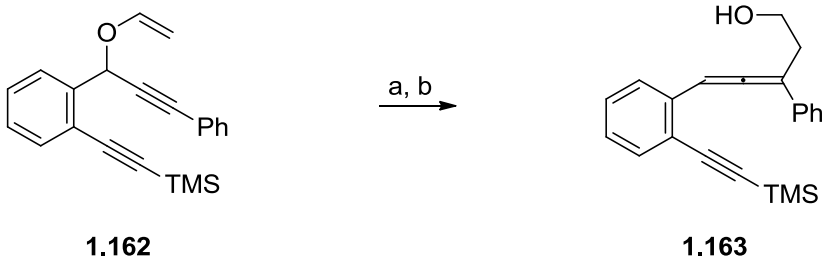


Reagents and Conditions: (a) TA-Au (3%), CH_2Cl_2, rt; (b) $NaBH_4$, MeOH, **1.161**: 33%.

Scheme 1.39: The Schmittel Cyclisation at Room Temperature

The 1,3-rearragnement of propargyl ether **1.158** would produce the trisubstituted allene **1.159**. In the presence of the photocyclisation condition (**Scheme 1.37)**, the diradical intermediates proceeded *via* two alternative reaction paths which should induce the formation of **1.161** and **1.160**. Notably, the TA-Au catalysed conditions produced **1.161** exclusively as the cyclisation product. One possible explanation for this might be the mild reaction conditions that preferred the aromatic cyclisation instead of the elimination (formation of **1.160**), emphasising the greatly improved selectivity of this method when compared with thermal and photo conditions. Altering the alkyne termini substituents from Ph to TMS enabled the successful isolation of the suggested allene intermediate **1.163**, which supplied

additional concrete evidence for the proposed mechanism and the rare reactivity of TA-Au (activation of the alkyne over the allene).



1.162 **1.163**

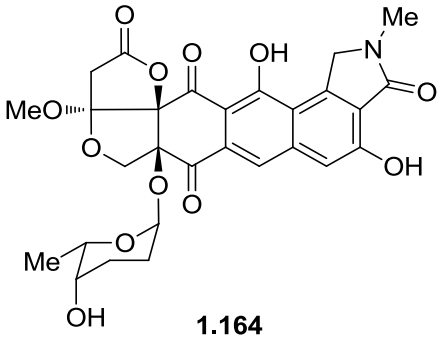
Reagents and Conditions: (a) TA-Au (3%), rt, CH_2Cl_2; (b) $NaBH_4$, MeOH, **1.163**: 23%.

Scheme 1.40: Confirmed Allene Intermediate

1.1.7. A Novel Cyclisation by Parsons *et al.*

1.1.7.1. *Studies Towards the Total Synthesis of Lactonamycin*

Matsumoto *et al.*[134] were the first to report the propitious antibiotic Lactonamycin **1.164** from *Streptomyces rishiniensis* cultures.



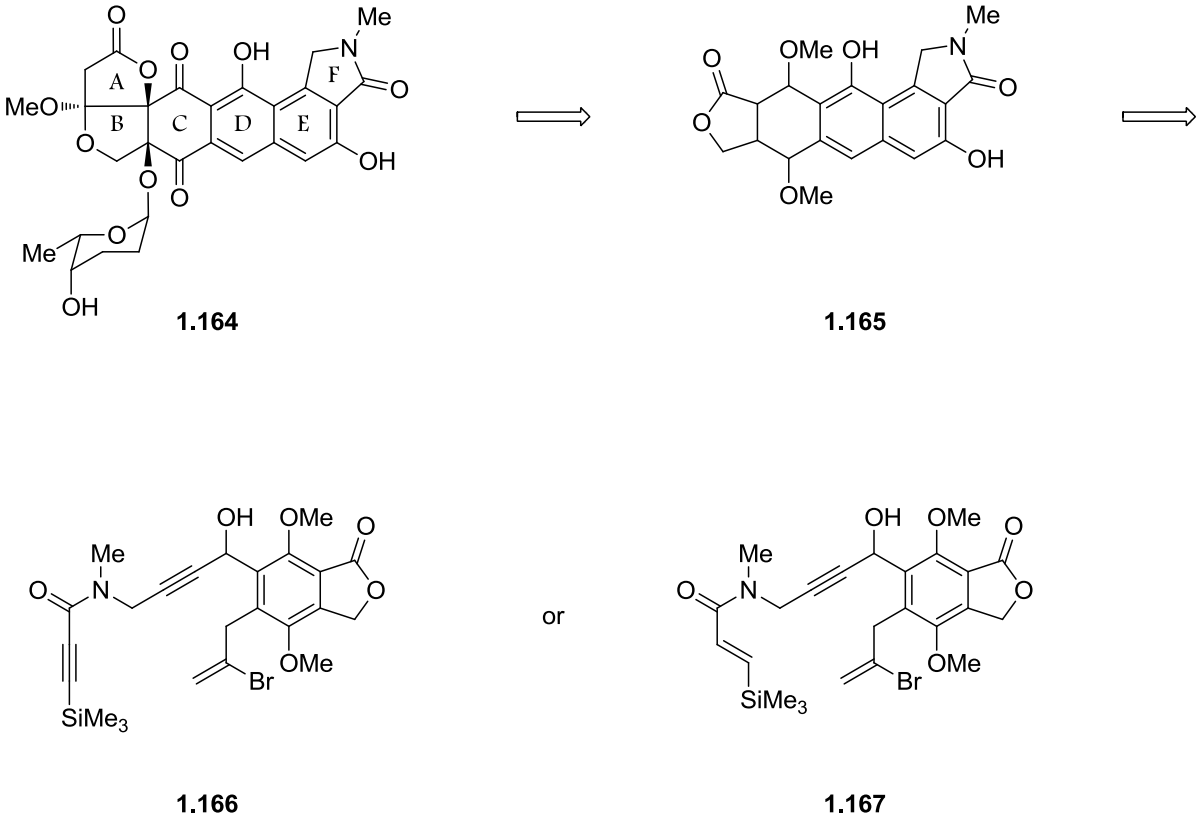
1.164

Figure 1.6: Lactonamycin

Lactonamycin **1.164** exhibits a plethora of biological activities with potential medicinal use. Most prominent of these, is the potent activity demonstrated against methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE).[135]

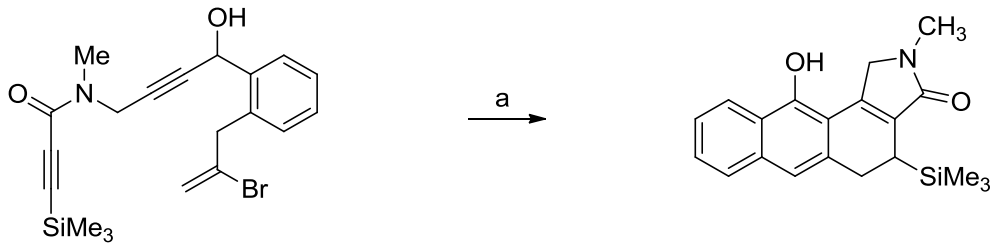
Additionally, the antibiotic displays antitumor activity against a number of malignant cancerous cell lines.

As a result of its complex chemical structure and conspicuous biological activity, many research groups have worked on the synthesis of lactonamycin in the laboratory.[136] However, achievements of this kind are rare and only one total synthesis has been accomplished to date.[137] The Parsons *et al.* has been concerned with the total synthesis of lactonamycin for several years and initially aimed to acquire the construction of the core CDEF fused ring structure.[138,139] The selected retrosynthetic approach is illustrated in **Scheme 1.41** below.



Scheme 1.41: Retrosynthetic Analysis of Lactonamycin by Parsons *et al.*[138,139]

Advanced intermediate **1.165** could be accessed by a single synthetic manipulation of **1.166** or **1.167**. In order to test the feasibility of the above cascade sequence, a model system **1.168** was synthesised (**Scheme 1.42**) The amide **1.168** was constructed with the aim of conducting either a palladium[140] or radical[141] cascade sequence[142] to form the structurally complex core CDEF fused ring structure of lactonamycin **1.164**.



1.168 **1.169**

Reagents and Conditions: (a) Benzene, radical initiator, reflux, time, yield, see **Table 1.5**.

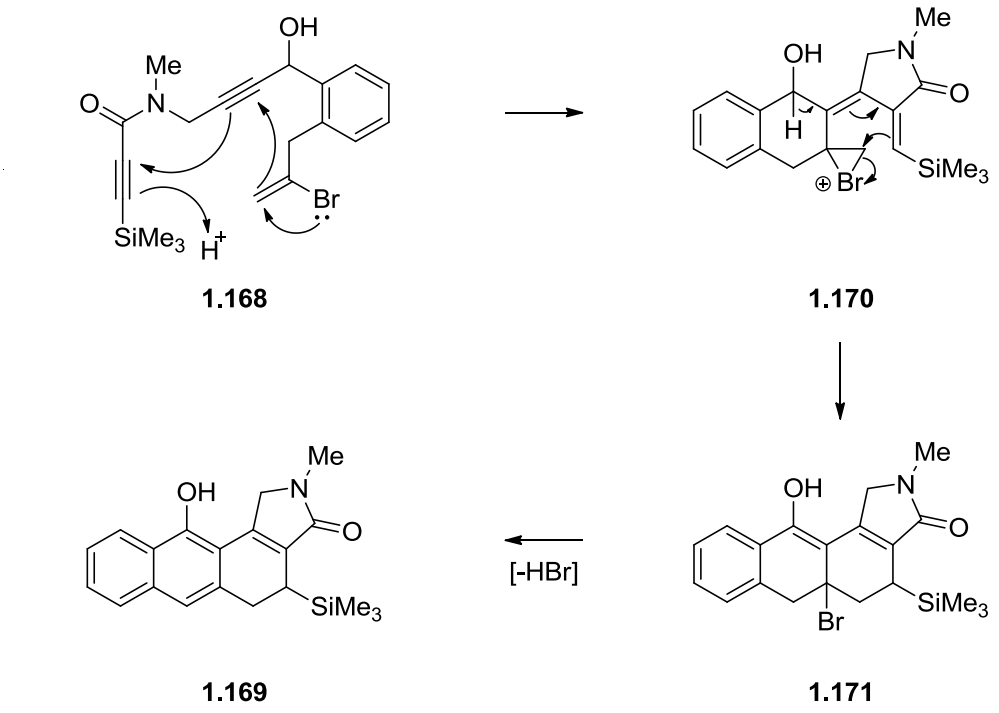
Scheme 1.42: Thermal Cyclisation of Precursor **1.168**

Entry	Radical initiator	Time (h)	Yield (%)
1	*n*-BuSnH/AIBN	11	14
2	$(Me_3Si)_3SiH$	72	22

Table 1.5: Radical Cyclisations of **1.168**

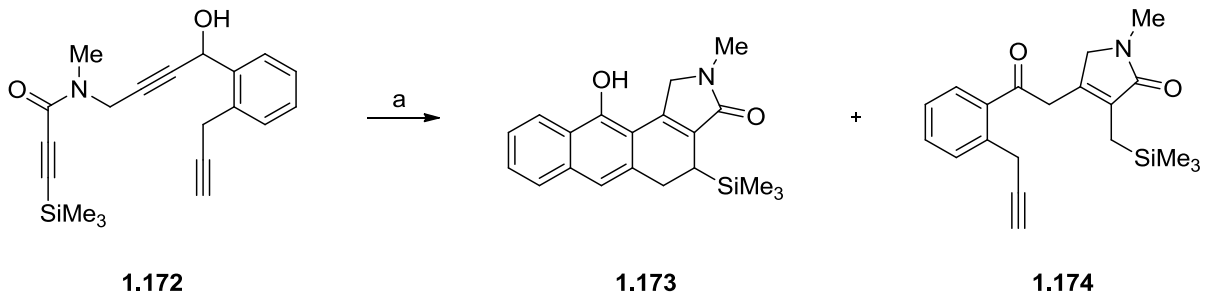
Two contrasting cyclisation conditions were administered to the material, resulting in a higher yield in tris(trimethylsilyl)silane than tri-*n*-butyltin hydride. However, both reactions were notably effected by excessive decomposition. A further study on thermal stability employed the technique of boiling **1.168** alone in benzene for 40 hours.[143] Most interestingly, this procedure gave a higher yield (26%) than any of the radical initiators previously used. This process revealed that the reagents used in the palladium or radical mediated cyclisations accounted for the decomposition. Subsequently, it was concluded that the reaction was thermally activated which led to the testing of a variety of solvents and temperatures. The model alkyne **1.168** was heated under reflux in toluene for 24 hours which afforded the desired tetracyclic compound **1.169** in 50% yield. Furthermore, in the presence of an acid trap (1-epoxyhexene) the yield of the reaction was advanced to 76%.

Originally, it was proposed that the cyclisation may have occurred *via* an acid-catalysed pathway. This was explained by the possible formation of hydrogen bromide under the reaction conditions.



Scheme 1.43: Proposed Acid-Catalysed Mechanism for the Formation of Compound **1.169**

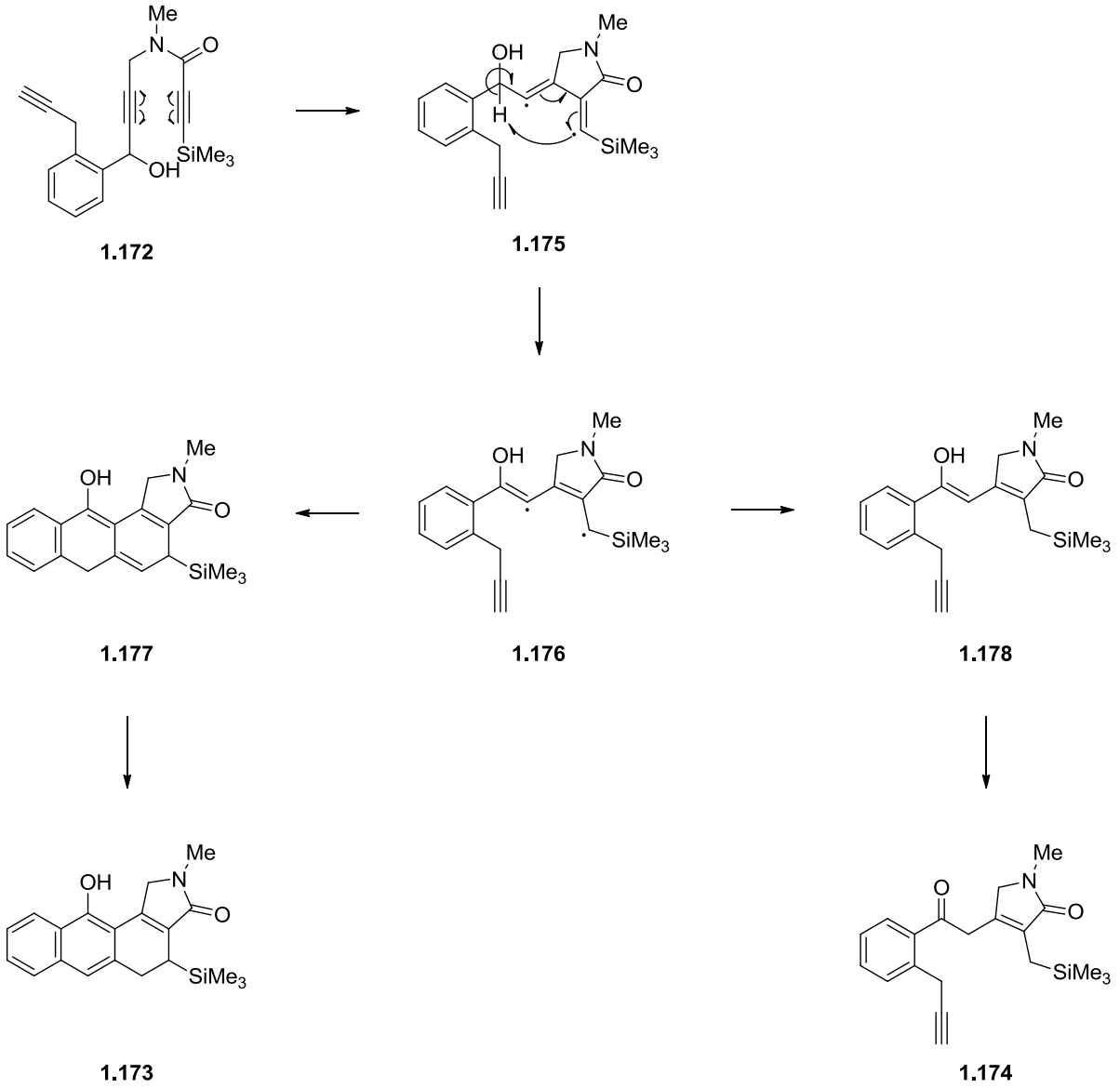
However, as mentioned previously when 1-epoxyhexene was added to the reaction mixture, the yield of the product was increased. As a result, an acid catalysed pathway was likely to be discounted. In order to substantiate this hypothesis, the cyclisation reaction of compound **1.172** was examined.[144] In this particular test, the generation of acid was not possible during the reaction. Consequently, if the reaction was acid catalysed then it would yield no product. On the contrary, in the absence of acid scavengers thermolysis of **1.172** in toluene furnished two new products.



Reagents and Conditions: (a) Toluene, reflux, 0.1M, 6h, **1.173**: 76%, **1.174**: 9%.

Scheme 1.44: Thermal Cyclisation of Precursor **1.172**

The isolation of compound **1.173** disproved the previous acid-catalysed theory, as bromine was not present in the molecule to produce catalytic quantities of hydrogen bromide in solution. Of particular interest, was the unexpected formation of product **1.174**. Its structure disclosed that the lower alkynyl portion in **1.172** failed to participate in the cyclisation and that two extra hydrogen atoms were incorporated during the course of the reaction. As a result of these observations, the mechanism in **Scheme 1.45** was put forward.



Scheme 1.45: Postulated Mechanism for the Formation of Compounds **1.173** and **1.174**

In the proposed mechanism, alkyne **1.172** cyclises to produce a concentration of bi-radical **1.175** which in succession could give bi-radical **1.176** by intramolecular 1,5-hydrogen atom abstraction and tautomerism. The bi-radical **1.176** reacted intramolecularly, yielding

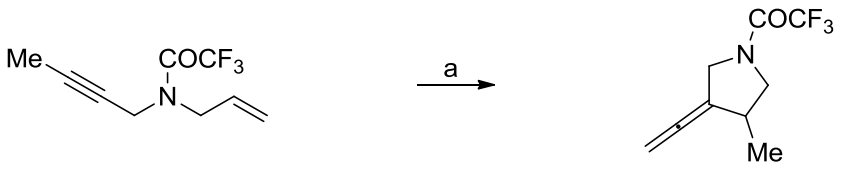
tetracycle **1.177** followed by isomerisation to phenol **1.173**. On the other hand, the bi-radical **1.176** could hydrogen-abstract from the solvent to generate enol **1.178** which is in equilibrium with the observed product **1.174**.

1.2. Ene Reactions Involving Triple Bonds

1.2.1. The Propargylic Ene Reaction

The ene reaction is mechanically linked to the well-known and more commonly applied Diels-Alder reaction, proceeding *via* a cyclic transition state comprising of six electrons. The intramolecular ene reaction is a well-known procedure,[145] however, there are just a few cases in the literature where the "ene" component is an alkyne with propargyl hydrogen instead of an alkene with an allylic hydrogen. The propargylic ene reaction generates an allene, which may engage in supplementary reaction in a tandem mode.

In 1973, Oppolzer identified the first propargylic ene reaction.[146] The reaction illustrated below occurred at a significantly reduced temperature than the equivalent 1,6-dialkene ene-cyclisations.



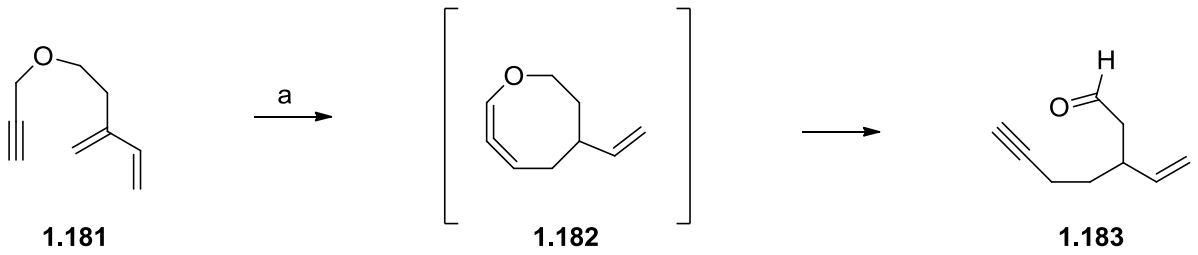
1.179 **1.180**

Reagents and Conditions: (a) Neat, 210 °C, 2h, 43%.

Scheme 1.46: First Example of Propargylic-Ene Reaction by Oppolzer *et al.*[146]

A mechanistic explanation was not put forward for the above reaction. However, it was suggested that the reaction occurs *via* an ene-mechanism.

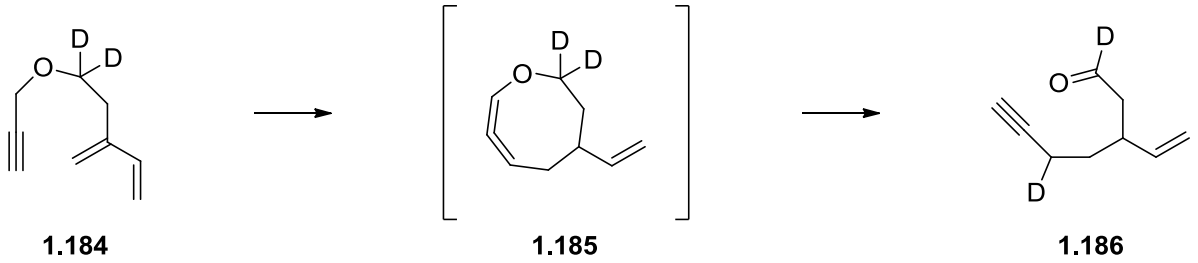
In 1988, Shea *et al.*[147] identified an unfamiliar by-product from the attempted intramolecular Diels-Alder reaction of dienyne **1.181**. The authors reported 1,2-cyclooctadiene **1.182** as the intermediate in this reaction, in account of a propargylic ene transformation of dienyne **1.181**.



Reagents and Conditions: (a) Neat, 420 °C, 12%.

Scheme 1.47: Work by Shea *et al.*[147]

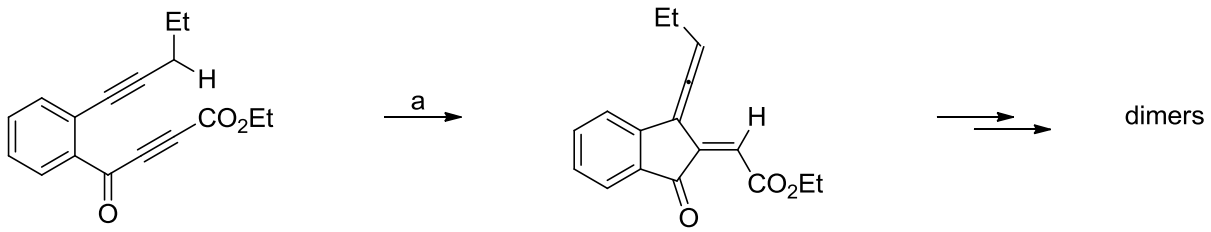
This mechanism for the conversion of **1.181** to **1.183** is supported by deuterium labelling experiments.[147]



Scheme 1.48: Deuterium-labelling Studies by Shea *et al.*[147]

A concerted propargylic-ene reaction with attendant 1,6-hydrogen abstraction produces cyclic allene **1.185**. The second step of the rearrangement was assumed to proceed through a retro-hetero ene fragmentation consisting of a 1,5-hydrogen abstraction step.[147]

In 2003, Pérez proposed a propargylic ene reaction as the decomposition route for a 1,6-diyne substrate that was being examined in Pd-catalysed [2+2+2] cycloadditions with benzene.[148] After standing at room temperature, **1.187** was converted into a compound with the assigned structure of **1.188**. Pérez and co-workers did not identify any spectral data for **1.188**, claiming that it "*finally evolved into a mixture of dimers*."



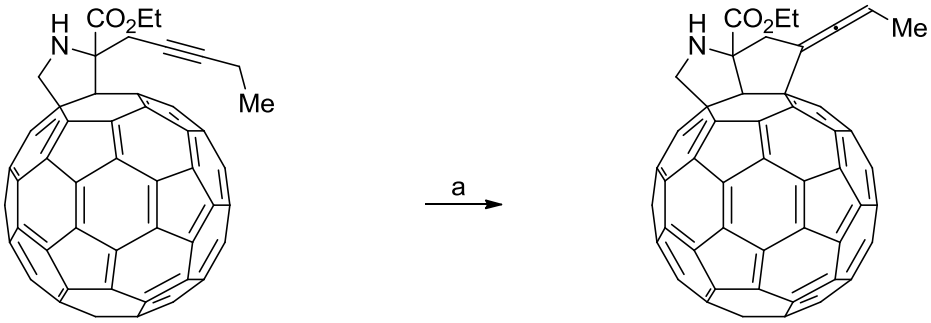
1.187 **1.188**

Reagents and Conditions: (a) Neat, rt.

Scheme 1.49: Work by Pérez *et al.*[148]

Allene **1.188** is a highly reactive *s-cis* vinylallene, which accounts for the difficulty in it being isolated. In addition, vinylallenes are reactive dienes in Diels-Alder reactions.

In 2006, Altable and co-workers proposed an intramolecular ene reaction of 1,6-fullerenynes.[149] The authors were aiming to extend the [2+2] cycloaddition of 1,6-fullerenynes to produce cyclobutene derivatives to contain non-terminal alkynes. Instead, they discovered efficient formation of allene derivatives (**Scheme 1.50**).

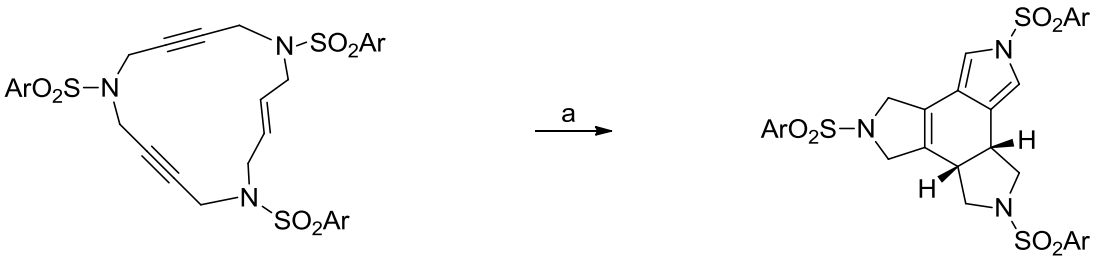


1.189 **1.190**

Reagents and Conditions: (a) PhCl, reflux, 3h, 99%.

Scheme 1.50: Work by Altable *et al.*[149]

In 2010, Roglans and co-workers reported a domino process combining an ene reaction between two alkynes and a Diels-Alder cycloaddition of the vinylallene formed. The process accounts for the thermally induced cycloisomerisation of cyclic enediyne **1.191** to give fused tetracycle **1.192**.[150]



1.191 **1.192**

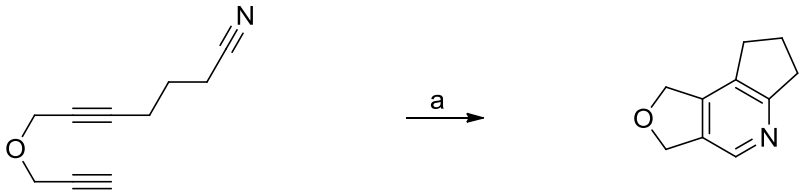
Ar = 2,4,6-triisopropylbenzene

Reagents and Conditions: (a) Toluene, reflux, 30h, 32%.

Scheme 1.51: Work by Roglans *et al.*[150]

The addition of a excess of 1,4-cyclohexadiene to the reaction mixture was found to increase the yield of the above reaction to 77% yield.[150] Initially, this discovery led the authors to propose that a bi-radical mechanism is in operation, comparable to that suggested by Parsons *et al*.[138,139] for their reaction. Nonetheless, EPR studies carried in the presence of radical traps were unsuccessful in confirming the presence of radical intermediates and alternatively, a propargylic-ene mechanism was proposed.[150]

Recently, Danheiser *et al.*[151] reported the use of an intramolecular cyclotrimerisation between two alkynes and a cyano group for the synthesis of substituted pyridines. A selected example is illustrated below (**Scheme 1.52**).

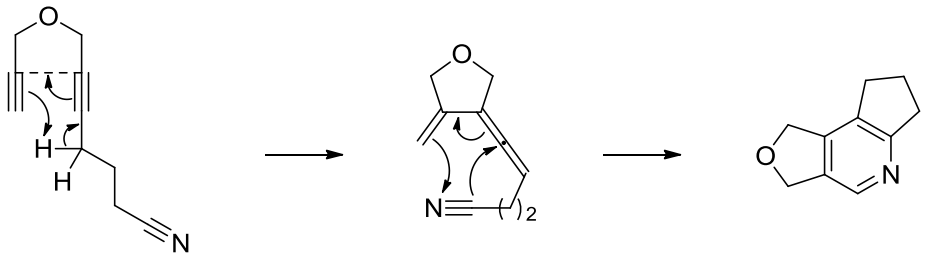


1.193 **1.194**

Reagents and Conditions: (a) Toluene, 0.1M, 160 °C, 21h, 71%.

Scheme 1.52: Work by Danheiser *et al.*[151]

The proposed mechanism involves a intramolecular propargylic-ene reaction between the 1,6-diyne with consequent Diels-Alder cycloaddition of the resulting vinylallene with the cyano group (**Scheme 1.53**).[151]



1.193 **1.195** **1.194**

Scheme 1.53: Proposed Mechanism Postulated by Danheiser *et al.*[151]

Chapter 2.

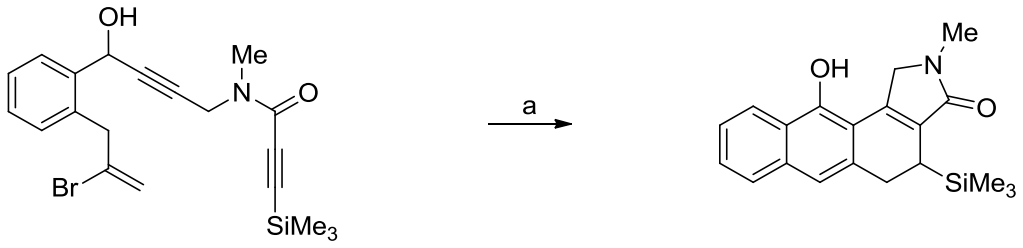
Results & Discussion

The development of novel strategies equips the synthetic chemist with techniques to synthesise interesting drug-like molecules. However, due to the complexity of many pharmaceutical drug molecules, long multi-step syntheses are necessary to construct the final compound. As a result, large amounts of reagents, solvents and energy are required, leading to a substantial quantity of waste production at each stage of synthesis. This has instigated growth in the research and development of greener tandem reactions, which conjoin multiple steps in a one-pot process, for the synthesis of complex organic molecules. The Parsons *et al.* recently developed a novel thermal cyclisation reaction as described in **Chapter 1**. This reaction could generate a bi-radical species and after being trapped with a suitable alkene or alkyne, could lead to the formation of tetracyclic molecules comprising heterocyclic cores. Therefore, we wish to further investigate this novel reaction and develop tandem reaction methodology around it.

2.1. Novel Cyclisation of 1,6-Diyne 2.1 for the Generation of Tricycle 2.2

2.1.1. Outline of Investigation

The aim of this DPhil research project was to devise and execute a series of experiments with the intention of gaining a better mechanistic understanding of the novel thermal cyclisation discovered by Parsons *et al.*[138,139] (**Scheme 2.1**).

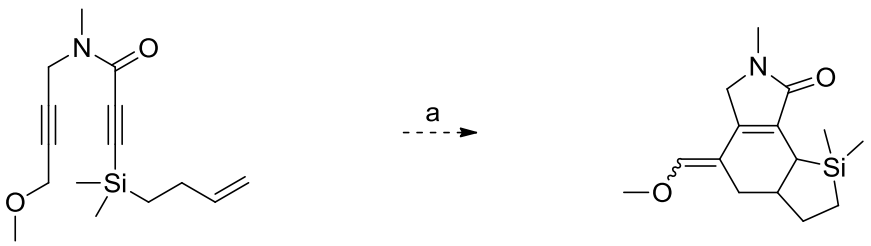


1.179 **1.180**

Reagents and Conditions: (a) Toluene, reflux, 76%.

Scheme 2.1: Original Cyclisation Discovered by Parsons *et al*.[138,139]

To further investigate the mechanism and scope of the cyclisation, the model system **2.1** was proposed (**Scheme 2.2**). Removal of the aromatic portion of the precursor and conversion of the alcohol to an ether linker was used to increase the versatility of the cyclisation model. These structural modifications would enable greater diversifications and more widely applicable methodology for the construction of polycyclic systems.

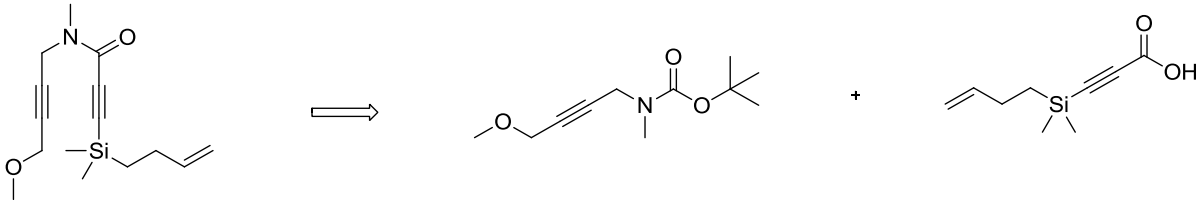


2.1 **2.2**

Reagents and Conditions: (a) Toluene, reflux.

Scheme 2.2: Aim within this Thesis.

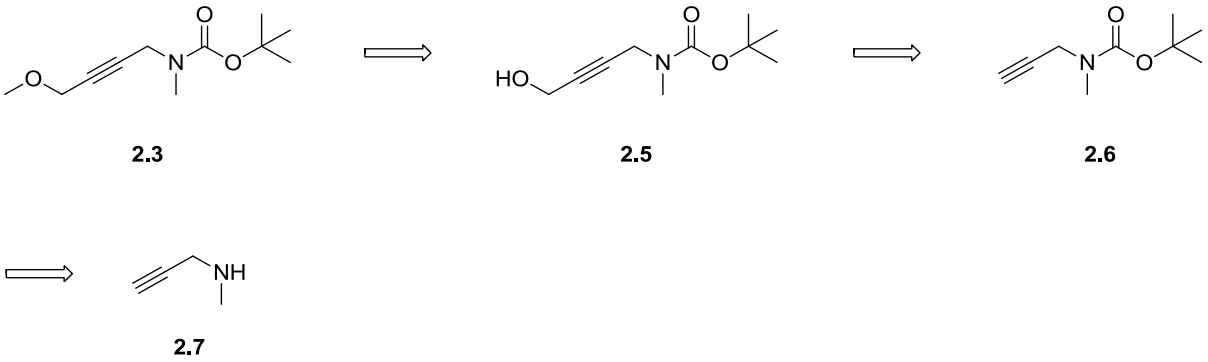
An overview of our retrosynthetic plan is depicted in **Scheme 2.3**. In this analysis, cyclisation precursor **2.1** was disconnected at the amide linkage. This process revealed the carbamate fragment **2.3** and the carboxylic acid fragment **2.4** as the first target of our synthesis.



2.1 **2.3** **2.4**

Scheme 2.3: Retrosynthetic Analysis of Cyclisation Precursor **2.1**

The retrosynthetic approach for the coupling precursor **2.3** is depicted in **Scheme 2.4** below.



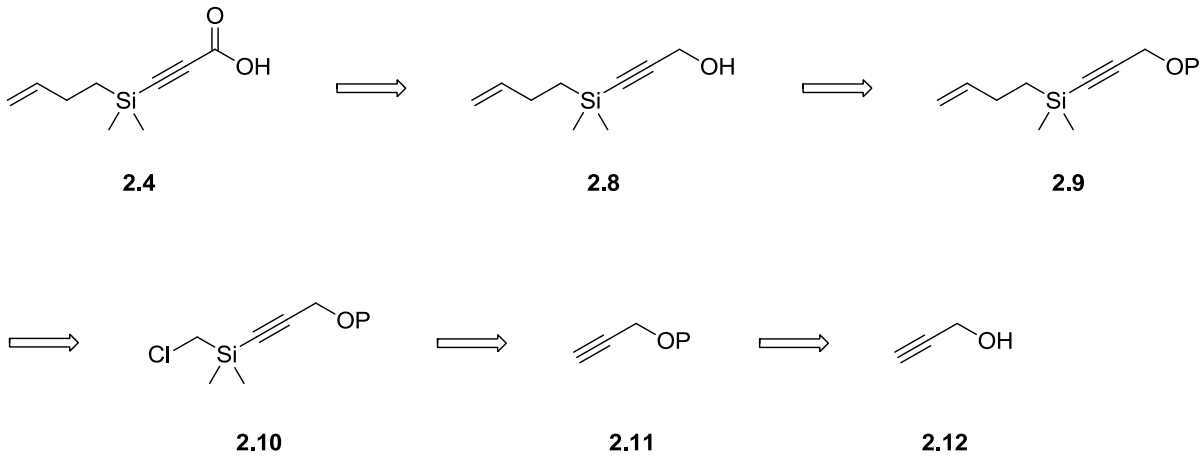
2.3 **2.5** **2.6**

2.7

Scheme 2.4: Retrosynthetic Analysis of the Carbamate Fragment **2.3**

Deprotonation of the *N*-Boc amine **2.6** and subsequent quenching with paraformaldehyde should afford the propargylic alcohol **2.5**. This can be manipulated to form the methyl ether **2.3**, ready for coupling with carboxylic acid fragment **2.4** to form the cyclisation precursor **2.1**.

In addition, the carboxylic acid fragment **2.4** can be readily synthesised by oxidation of the deprotected alcohol **2.8**. The protected alcohol **2.9** can be generated by reaction of alkyl chloride **2.10** and the Grignard reagent derived from allyl bromide. Alkyl chloride **2.10** can be easily synthesised by deprotonation of the alkyne **2.11** and subsequent quenching with chloro(chloromethyl) dimethylsilane. Furthermore, compound **2.11** can be obtained from commercially available propargyl alcohol **2.12** (**Scheme 2.5**).

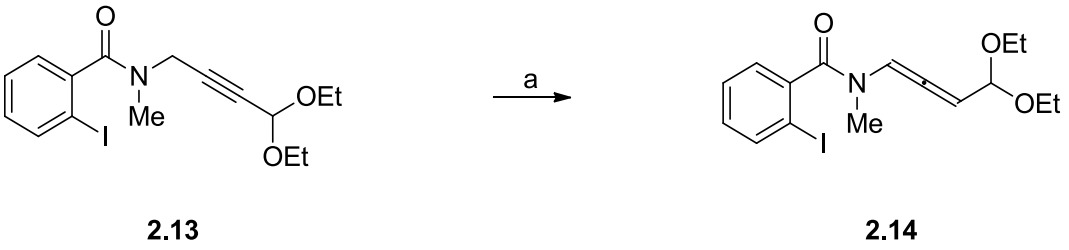


Scheme 2.5: Retrosynthetic Analysis of Carboxylic Acid Fragment **2.4**

2.1.2. Synthesis of Cyclisation Precursor 2.1

2.1.2.1. *Investigation of Nitrogen Protection/Deprotection Sequence*

It was necessary to protect *N*-methylpropargyl amine **2.7** at the nitrogen atom, in order to selectively deprotonate the terminal alkyne position (pKa ~ 25 in H_2O[152,153]). An additional factor to consider was that deprotonation by strong bases of the propargylic protons α to the nitrogen atom can be a contending possibility, as indicated in **Scheme 2.6** for a selected example.[154]

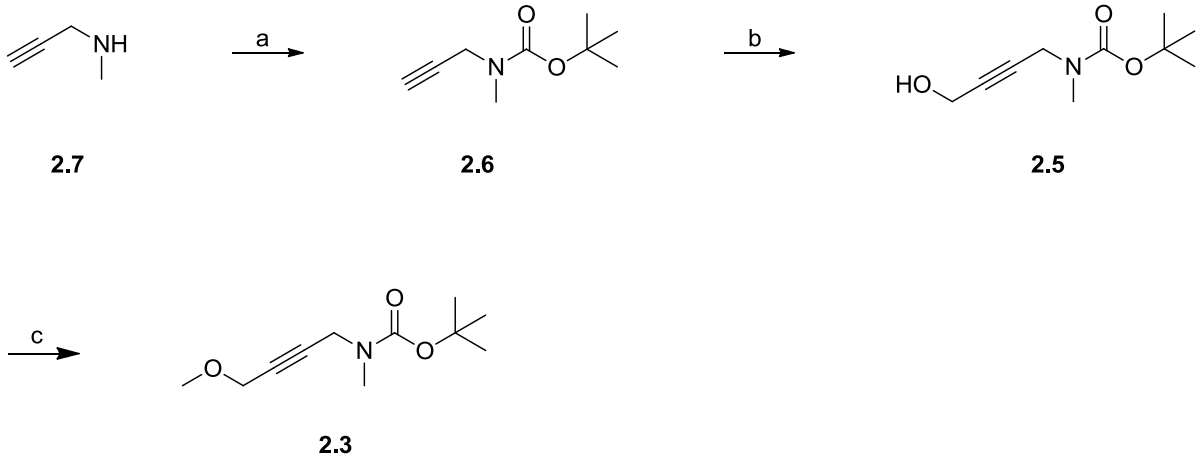


Reagents and Conditions: (a) *t*-BuOK, THF, 0 °C, 10 min., 88%.

Scheme 2.6: Work by Maddaluno *et al.*[154]

Therefore, the optimal protecting group for *N*-methylpropargyl amine **2.7** should replace the proton on the nitrogen atom whilst sterically hindering the propargylic position. One of the most frequently used groups for amine protection in organic synthesis is *tert*-butyl

carbamate.[155] This group is stable to nucleophilic, strong bases and is also moderately bulky. The adaptation of the Boc protecting group for the synthesis of amine fragment **2.3** is illustrated in **Scheme 2.7** below.



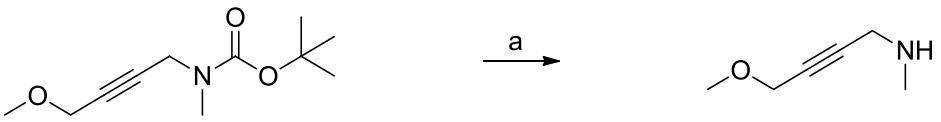
2.7 **2.6** **2.5** **2.3**

Reagents and Conditions: (a) Di-*tert*-butyl dicarbonate, pyridine, CH_2Cl_2, 0 °C to rt, 16h, 96%; (b) *n*-BuLi, THF then paraformaldehyde, -78 °C to rt, 16h, 78%; (c) MeI, KOH, DMSO, rt, 16h, 90%.

Scheme 2.7: The Use of Boc Protecting Group for the Synthesis of Amine Fragment **2.3**

Protection of *N*-methylpropargyl amine **2.7** with di-*tert*-butyl dicarbonate in the presence of pyridine afforded the *N*-Boc-*N*-methyl propargylamine **2.6** in near quantitative yield (96%).[139] The treatment of the *N*-Boc-*N*-methyl propargylamine **2.6** with *n*-butyllithium in THF, followed by subsequent addition of paraformaldehyde at -78 °C afforded the desired alcohol **2.5** in 78% yield.[139] Deprotonation of the alcohol **2.5** with sodium hydride and treatment with methyl iodide afforded the required methyl ether **2.3** in 67% yield.[156] More encouraging results were obtained when propargylic alcohol **2.5** was treated with potassium hydroxide in DMSO, followed by subsequent addition of methyl iodide (90%).[157]

The next step in the synthetic sequence was the removal of the *N*-Boc protecting group. Various methods were employed for the removal of the *N*-Boc protecting group and these are shown in **Table 2.1**.



2.3 **2.15**

Reagents and Conditions: (a) Reagent, solvent, temperature, yield, see **Table 2.1**

Scheme 2.8: Attempted Boc-Deprotection

Entry	Reagent	Solvent	Temperature (°C)	Yield (%)[a]
1	TFA	CH_2Cl_2	0-rt	DM[b]
2	2M HCl	Et_2O	0-rt	48
3	2M HCl	EtOAc	0-rt	51
4	4M HCl	Dioxane	0-rt	71
5	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0-rt	-
6	$MgBr_2$	CH_2Cl_2	0-rt	-
7	TMSCl	CH_2Cl_2	0-rt	-

[a] Yields of isolated products. DM[b] = decomposition of material

Table 2.1: Reagents Tested for Boc-Deprotection

Initial attempts at *N*-Boc deprotection utilised trifluoroacetic acid in dichloromethane.[158,159] Unfortunately, addition at 0 °C followed by stirring at room temperature for one hour led to complete decomposition of the reaction mixture. More promising results were obtained when a solution of hydrogen chloride in ethyl acetate was employed.[160] Treatment of the methyl ether **2.3** with a 2M solution of hydrochloric acid in ethyl acetate, followed by collection by vacuum filtration of the hydrogen chloride salt afforded a clean deprotection (51%). This result however was deemed unsatisfactory due to the high cost of *N*-methylpropargyl amine **2.7** which is needed at the start of the synthesis of precursor **2.3**. It was suggested that using $BF_3{\cdot}OEt_2$ and 4Å molecular sieves in dichloromethane followed by oxalic acid addition might increase the yield.[161] However, entries 5, 6 and 7 suffered from a slow rate of reaction and the isolated products were contaminated with significant amount of impurities.[162,163] The

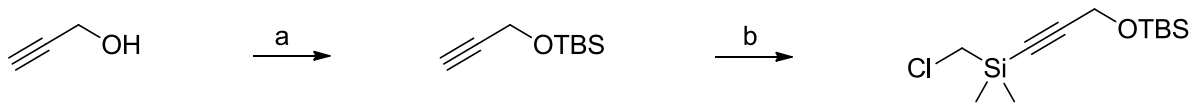
best results were obtained with a 4M solution of hydrogen chloride in dioxane which gave the hydrogen chloride salt of **2.15** in 71% yield. This material required no further purification.[164]

2.1.2.2. *Synthesis of Carboxylic Acid Fragment 2.4*

It was necessary to protect propargyl alcohol **2.12** at the oxygen atom, in order to selectively deprotonate the terminal alkyne position (pKa ~ 25 in H_2O[152,153]). Silyl ethers are often used as protecting groups for alcohols.[165] The reason for the wide popularity of silicon protecting groups is easily explained; they are readily formed and cleaved under mild conditions and their relative stability can be finely tuned by varying the substituents on silicon.

The commercially available *tert*-butyldimethylsilyl (TBS) chloride is often used as a silylating agent.[165] The derivatisation of alcohols as their *tert*-butyldimethylsilyl ethers has been recognised as one of the most useful protection methods since its introduction by Corey and Venkateswarlu in 1972.[166] This is in account of its easy installation and general stability to basic and mildly acidic conditions. *tert*-Butyldimethylsilyl ethers are also stable to column chromatography and they are stable below 0 °C to strong non-protic bases such as *n*-alkyllithiums.

The adaptation of the TBS protecting group for the synthesis of alkyl chloride **2.17** is illustrated in **Scheme 2.9** below.



2.12 **2.16** **2.17**

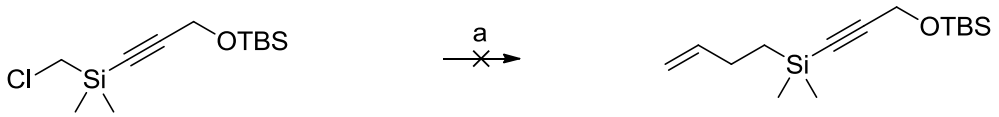
Reagents and Conditions: (a) *tert*-Butyldimethylsilyl chloride, imidazole, CH_2Cl_2, 0 °C to rt, 1h, 98%; (b) *n*-BuLi, THF then chloro(chloromethyl)dimethylsilane, -78 °C to rt, 16h, 85%.

Scheme 2.9: Synthesis of Alkyl Chloride **2.17**

The use of imidazole as an acid scavenger with *tert*-butyldimethylsilyl chloride in dichloromethane proved to be effective, and resulted in the mild conversion of propargyl alcohol **2.12** to *tert*-butyldimethylsilyl ether **2.16** in excellent yield (98%).[167] Treatment of silyl ether **2.16** with *n*-butyllithium in THF, followed by subsequent addition of

chloro(chloromethyl)dimthylsilane at -78 °C gave the desired alkyl chloride **2.17** in 85% yield.[139]

An attempted coupling of allylmagnesium chloride with alkyl chloride **2.17** was carried out. Unfortunately, none of the desired product was observed so the reaction was repeated using an alternative procedure. A reverse addition was attempted with the addition of the alkyl chloride **2.17** to allylmagnesium chloride. None of the desired product was observed and only starting material was recovered in these reactions.

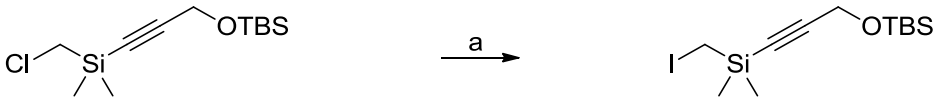


2.17 **2.18**

Reagents and Conditions: (a) Allylmagnesium chloride, THF, 0 °C to rt, 16h.

Scheme 2.10: Coupling Reaction of Alkyl Chloride **2.17** with Allylmagnesium Chloride

Having failed to find suitable conditions for the coupling of allylmagnesium chloride with alkyl chloride, our attention was directed towards exchange of the halogen atom for another. The equilibrium exchange of the halogen atom in alkyl halides for another halogen atom is known as the Finkelstein reaction.[168] Halide exchange is an equilibrium reaction yet the reaction can be driven to completion by taking advantage of differential solubility of halide salts, or by using a large excess of the halide salt. The classic Finkelstein reaction involves the conversion of an alkyl chloride or an alkyl bromide to an alkyl iodide by the addition of sodium iodide in acetone.[169]

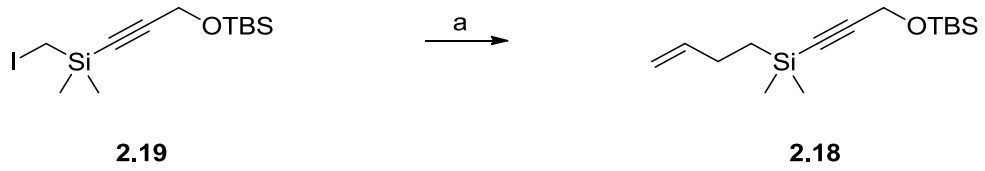


2.17 **2.19**

Reagents and Conditions: (a) NaI, acetone, rt, 16h, 91%.

Scheme 2.11: Conversion of Alkyl Chloride **2.17** to an Alkyl Iodide **2.19**

The coupling of alkyl iodide **2.19** with a 2M solution of allylmagnesium chloride in THF was used as the test reaction (**Scheme 2.12**). In the absence of a catalyst, the reaction yielded only 5% of the required product **2.18**.

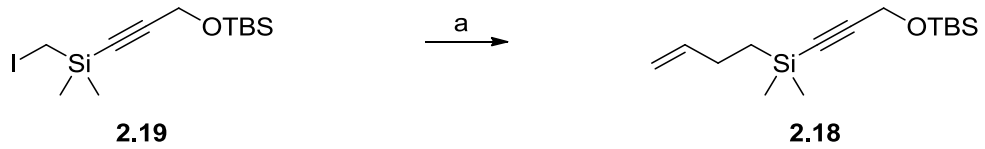


2.19 **2.18**

Reagents and Conditions: (a) Allylmagnesium chloride, THF, 0 °C to rt, 16h, 5%.

Scheme 2.12: Coupling Reaction between Alkyl Iodide **2.19** and Allylmagnesium Chloride

Considering that efficient alkyl–alkyl coupling reactions had been difficult to achieve, the judicious choice of catalyst and reaction conditions were employed to circumvent this problem. Kambe *et al.*[170,171,172] demonstrated that non-activated alkyl halides could be coupled to alkyl Grignard reagents in high yields in the presence of various copper salts. Following these reported conditions, coupling reactions were repeated in the presence of CuCl, however no coupling product was formed. The addition of CuI (used by Fuchikami *et al.*[173]) to couple alkyl iodide **2.19** with Grignard reagent also failed to yield the desired compound. Furthermore, Baeckvall *et al.*[174] demonstrated that Grignard reagents could efficiently undergo CuCN catalysed coupling reactions with alkyl halides. Following these reported conditions, one equivalent of cuprous cyanide was used to attempt to afford the corresponding lower-order cyanocuprate. The cuprate was then reacted with alkyl iodide **2.19** to yield the desired compound **2.18**. Nevertheless, these conditions also afforded none of the desired compound. The soluble copper reagent Li_2CuCl_4 which is known to couple terminal alkyl halides with long chain terminal unsaturated Grignard reagents was also used as a catalyst.[175] After having little success with this catalyst (Entry 6, **Table 2.2**), the Grignard addition was tried again under various conditions and the results are shown in **Table 2.2** below. The yields were over 75% for reactions in THF at 0 °C but lower for reactions in diethyl ether (Entries 7 and 8 respectively, **Table 2.2**). A catalyst loading of 50 mol% was sufficient to give a yield of 77%.



2.19 **2.18**

Reagents and Conditions: (a) Allylmagnesium chloride, catalyst, solvent, temperature, yield, see **Table 2.2**.

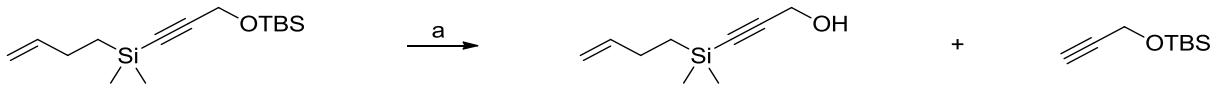
Scheme 2.13: Coupling Reaction between Alkyl Iodide **2.19** and Allylmagnesium Chloride

Entry	Catalyst	Solvent	Temperature (°C)	Yield (%)[a]
1	-	THF	0-rt	5
2	CuCl	THF	-78-rt/-30-rt/0-rt	0
3	CuI	THF	-78-rt/-30-rt/0-rt	0
4	CuCN	THF	-78-rt/-30-rt/0-rt	0
5	Li_2CuCl_4 (5-100 mol%)	THF	-78-rt	0
6	Li_2CuCl_4 (5 mol%)	THF	0-rt	16
7	Li_2CuCl_4 (50 mol%)	THF	0-rt	77
8	Li_2CuCl_4 (50 mol%)	Et_2O	0-rt	71

[a] Yields of isolated products

Table 2.2: Catalysts Tested for the Coupling Reaction

The next step in the synthetic sequence was the removal of the TBS protecting group. A wide variety of acidic reagents were used for the cleavage of *tert*-butyldimethylsilyl, including HOAc/THF/H_2O,[176] mineral acids such as HCl[177] and H_2SO_4,[178] TsOH,[179] HF/CH_3CN[180] and TFA.[181] These reactions proceeded to completion within 1 hour. The reaction mixture was monitored by thin layer chromatography. The isolated product indicated that removal of the but-3-en-1-yl dimethylsilane group had predominantly occurred instead of the desired selective deprotection of the silyl motif. Deprotection with a less acidic reagent was then pursued. However, stirring **2.18** in MeOH in the presence of PPTS (pKa = 5.21 in H_2O[182]) furnished the same product **2.16** in 28% yield (**Table 2.3**).[183]



2.18 **2.20** **2.16**

Reagents and Conditions: (a) Reagent, solvent, temperature, yields, see **Table 2.3**.

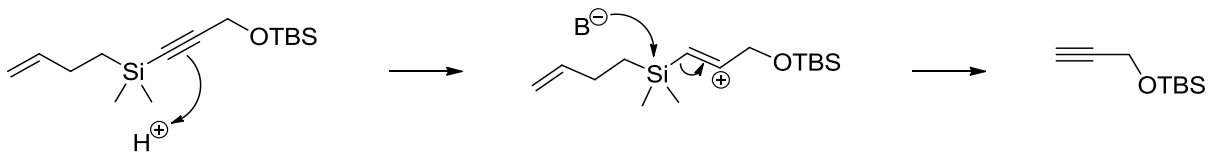
Scheme 2.14: Attempted TBS-Deprotection

Entry	Reagent	Solvent	Temperature (°C)	**2.20** (yield)[a]	**2.16** (yield)[a]
1	HCl	MeOH	0-rt	trace	37
2	H_2SO_4	MeOH	0-rt	trace	32
3	TsOH	MeOH	0-rt	trace	32
4	TFA	THF	0-rt	trace	35
5	HF	CH_3CN	0-rt	trace	30
6	HF	THF	0-rt	trace	40
7	AcOH	THF/H_2O	0-rt	trace	38
8	PPTS	MeOH	0-rt	trace	28

[a] Yields of isolated products

Table 2.3: Attempts to remove the *tert*-Butyldimethylsilyl Group

A possible cause for the undesired cleavage of the silyl group could be its ability to stabilise a *β*-cation (*β*-silicon effect[184,185]) which would be generated from the protonation of the alkyne in **2.18** as depicted in **Scheme 2.15**. Subsequent attack by the conjugate base on the silicon group would then furnish **2.16**.

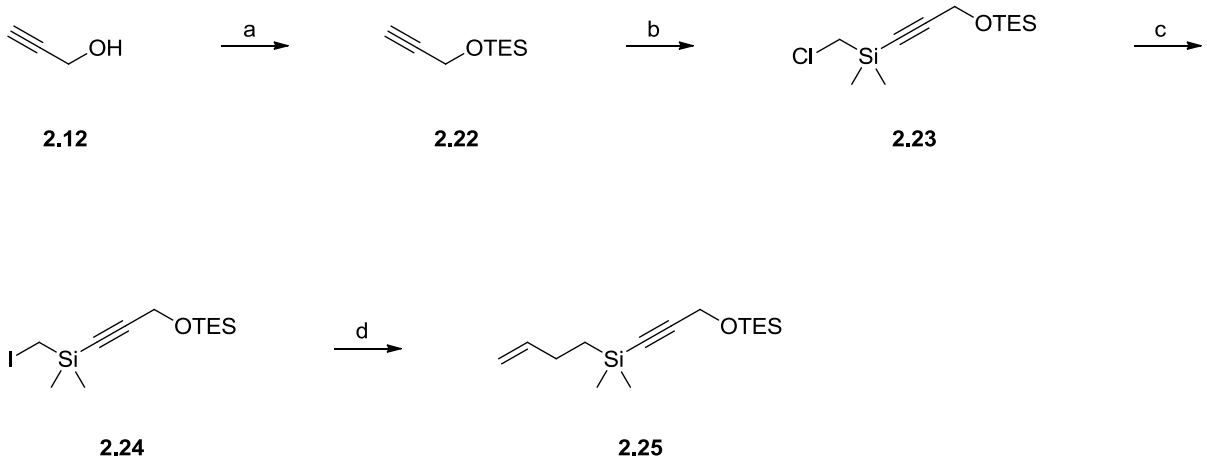


2.18 **2.21** **2.16**

Scheme 2.15: Possible Mechanism for the Elimination of the Silyl Group

Deprotection of TBS ethers is not limited to acidic reagents: fluoride is also effective and the most popular reagent is tetrabutylammonium fluoride (TBAF).[186] The same result was also obtained when TBAF was employed in THF (41% yield of **2.16**).

Having observed the probable stability of the silyl ether, the propargyl alcohol **2.12** was protected with TES group. The TES group can be readily introduced and is facile to remove.[165] Furthermore, it is sufficiently stable to endure column chromatography and many organometallic reactions. The TES ethers are relatively less stable towards acid and base catalysed hydrolysis compared to TBS ethers.[165] The adaptation of the TES protecting group for the synthesis of silyl ether **2.25** is shown in **Scheme 2.16** below.

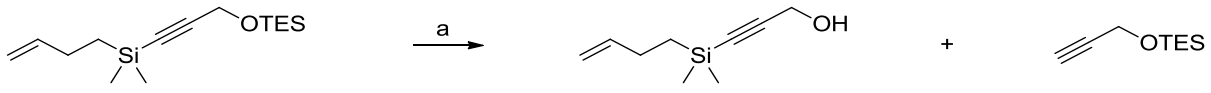


Reagents and Conditions: (a) Chlorotriethylsilane, imidazol, DMF, 0 °C to rt, 1h, 86%; (b) *n*-BuLi, THF then chloro(chloromethyl)dimethylsilane, -78 °C to rt, 16h, 85%; (c) NaI, acetone, rt, 16h, 88%; (d) Allylmagnesium chloride, Li_2CuCl_4, THF, 0 °C to rt, 16h, 80%.

Scheme 2.16: Synthesis of Silyl Ether **2.25**

The use of imidazole with chlorotriethylsilane in dimethylformamide proved to be effective and resulted in the mild conversion of propargyl alcohol **2.12** to triethylsilyl ether **2.22** in high yield (86%).[187] The but-3-en-1-yldimethyl(3-((triethylsilyl)oxy)prop-1-yn-1-yl)silane **2.25** was prepared from compound **2.22** by using an identical procedure to the preparation of but-3-en-1-yl(3-((tert-butyldimethylsilyl)oxy)prop-1-yn-1-l) dimethylsilane **2.18**.

The removal of triethylsilyl group was subsequently attempted with HCl in methanol.[188] The isolated product indicated that removal of the but-3-en-1-yldimethylsilane group had predominantly occurred instead of the desired deprotection. Attempts to prevent this unwanted product were unsuccessful and results are shown in **Table 2.4** below.



2.25 **2.20** **2.22**

Reagents and Conditions: (a) Reagent, solvent, temperature, yields, see **Table 2.4**.

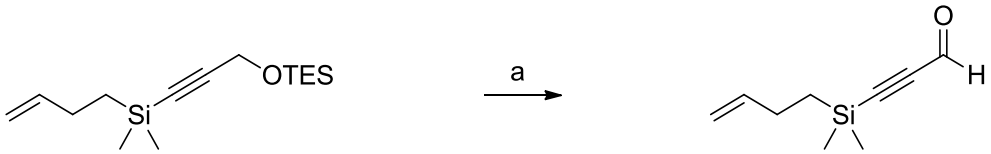
Scheme 2.17: Attempted TES-Deprotection

Entry	Reagent	Solvent	Temperature (°C)	**2.20** (yield)[a]	**2.22** (yield)[a]
1	HCl	MeOH	0-rt	trace	33
2	PPTS	MeOH	0-rt	trace	43
3	TBAF	THF	0-rt	trace	46
4	K_2CO_3	*i*-PrOH	0-rt	0	0
5	K_2CO_3	MeOH	0-rt	0	0

[a] Yields of isolated products

Table 2.4: Attempts to Remove the Triethylsilyl Group

Carefully chosen oxidative conditions allow for the selective removal of a silyl group from primary alcohol with the resulting free carbinol undergoing oxidation. Swern conditions have been employed for the conversion of primary TES ethers into aldehydes *via* the *in-situ* desilylation-oxidation of protected alcohol.[189] Unfortunately this procedure suffered from a slow rate of reaction (72 hours) and produced aldehyde **2.26** in poor yield (22%).



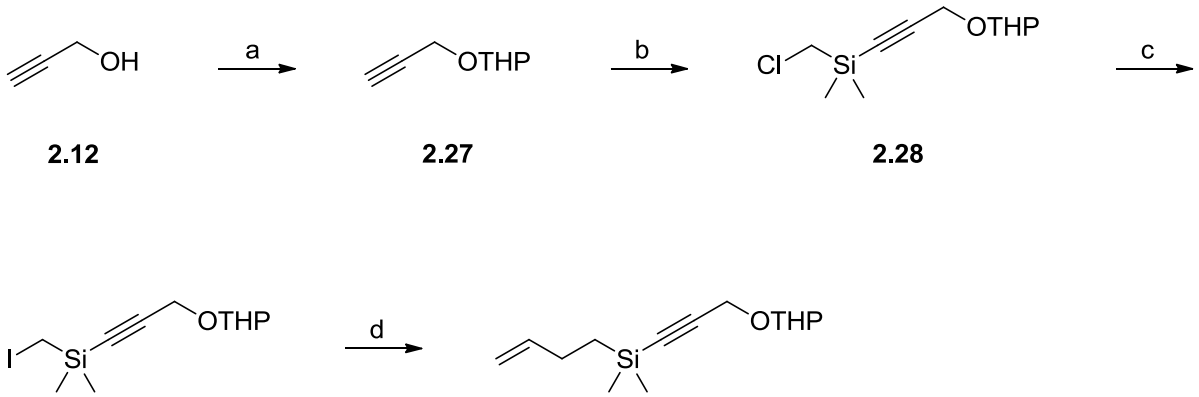
2.25 **2.26**

Reagents and Conditions: (a) $(COCl)_2$, DMSO, Et_3N, 72h, 22%.

Scheme 2.18: Oxidative Deprotection of TES-Ether

A more efficient method had to be sought and to this end a THP protecting group was suggested. Tetrahydropyranyl ethers were one of the first generally useful protecting groups for alcohols and they are still widely used today.[190] The particular merits of the THP group are its ease of introduction, the low cost of 3,4-dihydro-*2H*-pyran, its stability (in the absence of protic and Lewis acids) under a wide range of reaction conditions and its ease of removal. THP protection has disadvantages such as the complexity of the NMR spectra and the fact that diastereoisomers are formed on reaction with chiral alcohols.

The adaptation of the THP protecting group for the synthesis of THP ether **2.30** is shown in **Scheme 2.19** below.



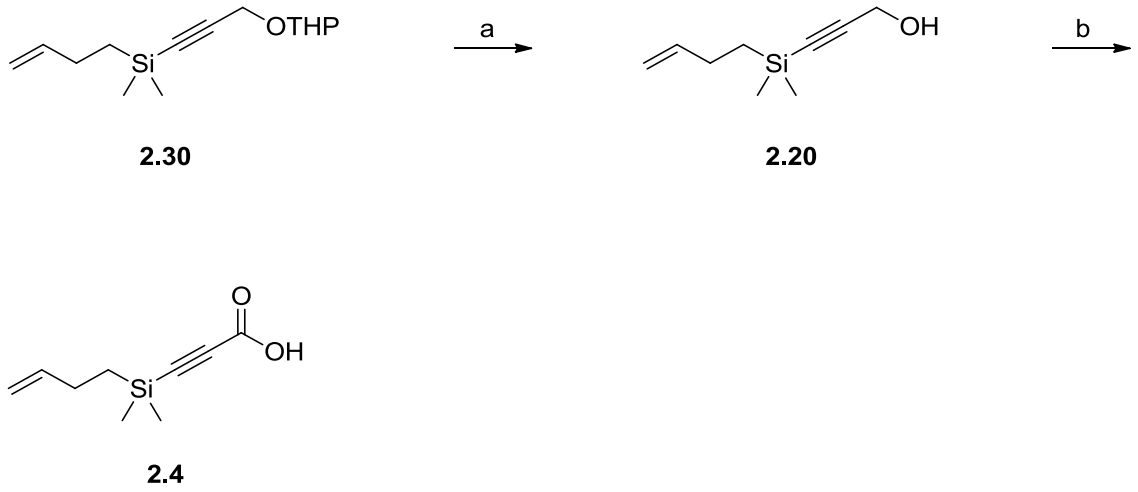
Reagents and Conditions: (a) 3,4-dihydro-*2H*-pyran, *para*-toluenesulfonic acid monohydrate, CH_2Cl_2, 0 °C to rt, 4h, 95%; (b) *n*-BuLi, THF then chloro(chloromethyl)dimethylsilane, -78 °C to rt, 16h, 89%; (c) NaI, Acetone, rt, 16h, 82%; (d) Allylmagnesium chloride, Li_2CuCl_4, THF, 0 °C to rt, 16h, 76%.

Scheme 2.19: The Use of THP Protecting Group for the Synthesis of THP Ether **2.30**

The use of *para*-toluenesulfonic acid as a catalyst with 3,4-Dihydro-2*H*-pyran in dichloromethane proved to be effective and resulted in the mild conversion of propargyl alcohol **2.12** to tetrahydropyranyl ether **2.27** in excellent yield (95%).[191] The but-3-en-1-yldimethyl(3-((tetrahydro-*2H*-pyran-2-yl)oxy)prop-1-yn-1-yl) silane **2.30** was prepared from compound **2.27** by using an identical procedure to the preparation of but-3-en-1-yl(3-((*tert*-butyldimethylsilyl)oxy)prop-1-yn-1-yl)dimethylsilane **2.18**.

Most Lewis acids cleave THP ethers and conditions are mild enough to allow retention of protecting groups that are otherwise labile in aqueous or alcoholic acid solutions. For

example, three equivalent of magnesium bromide in diethyl ether have been used to cleave THP ethers of primary alcohols.[192] Unfortunately, addition at 0 °C followed by stirring at room temperature for one hour led to complete decomposition of the reaction mixture. The attempted removal of THP group with PPTS in MeOH was tried and the required alcohol **2.20** was obtained in low yield (39%).[193] The alcohol **2.20** was oxidised with Jones' reagent to give the carboxylic acid **2.4** in 85% yield.

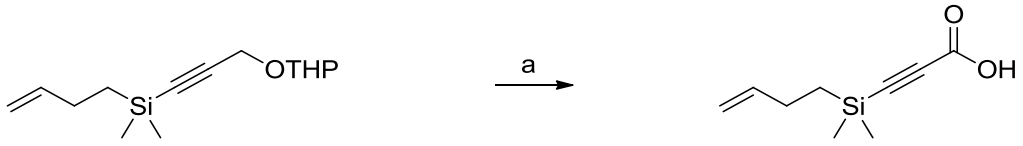


2.30 **2.20** **2.4**

Reagents and Conditions: (a) PPTS, MeOH, rt, 3h, then sat. aq. $NaHCO_3$, 39%; (b) CrO_3, H_2SO_4, H_2O, acetone, 0 °C to rt, 3h, 85%.

Scheme 2.20: Synthesis of Carboxylic Acid **2.4**

Regeneration of the protected group to the original functional group or its oxidized form is a useful transformation. The latter has been the focus of attention and a variety of methods have been reported.[194] Attempted oxidative deprotection of tetrahydropyranyl ether **2.30** with Jones' reagent was tried and desired carboxylic acid **2.4** was obtained in excellent yield (96%).



2.30 **2.4**

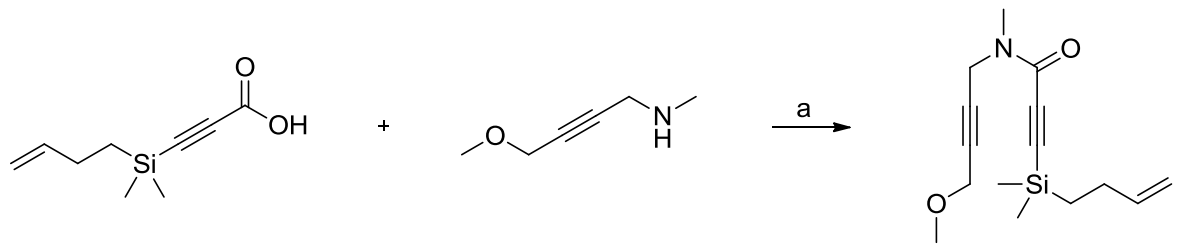
Reagents and Conditions: (a) CrO_3, H_2SO_4, H_2O, acetone, 0 °C to rt, 3h, 96%.

Scheme 2.21: Oxidative Deprotection of Tetrahydropyranyl Ether **2.30**

The reaction went to completion within 3 hours and the crude product was pure enough to be used directly in the next step. This method did not only reduce the required time for the synthesis but it also avoided column chromatography.

2.1.2.3. *Investigation of Amide Coupling*

The formation of amide **2.1** was subsequently investigated and to this ends various coupling reagents and additives[195] were tested as shown in **Table 2.5** below.



2.4 **2.15** **2.1**

Reagent and Conditions: (a) Et_3N, CH_2Cl_2, activating agent, yield, see **Table 2.5**.

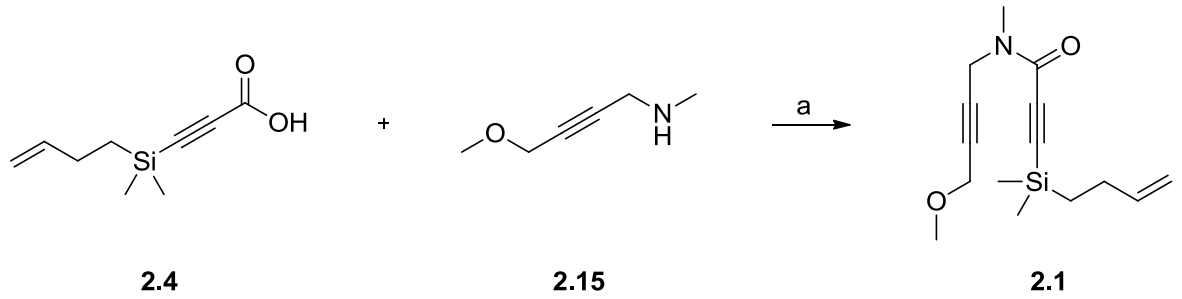
Scheme 2.22 Synthesis of Cyclisation Precursor **2.1**

Entry	Activating agent	Yield (%)[a]
1	Oxalyl Chloride / DMF	48
2	Oxalyl Chloride / DMAP	0
3	DCC	38
4	CDI	18
5	HBTU	38
6	DCC / HOBt	21
7	EDCl	33

[a] Yields of isolated products

Table 2.5: Different Activating Agents Tested for Amide Coupling

The -++best results were obtained with oxalyl chloride in the presence of a catalytic amount of DMF which gave amide **2.1** in 48% yield.[196] However, this result was deemed unsatisfactory due to the high cost of *N*-methylpropargylamine **2.7** which is required at the start of the synthesis of coupling precursor **2.15**. Therefore attention was directed to other reagents involved in the reaction, and different bases were screened for the amide coupling (**Scheme 2.23**).



2.4 **2.15** **2.1**

Reagent and Conditions: (a) Oxalyl chloride, $DMF_{(cat.)}$, CH_2Cl_2, base, yield, see **Table 2.6**.

Scheme 2.23: Synthesis of Cyclisation Precursor **2.1**

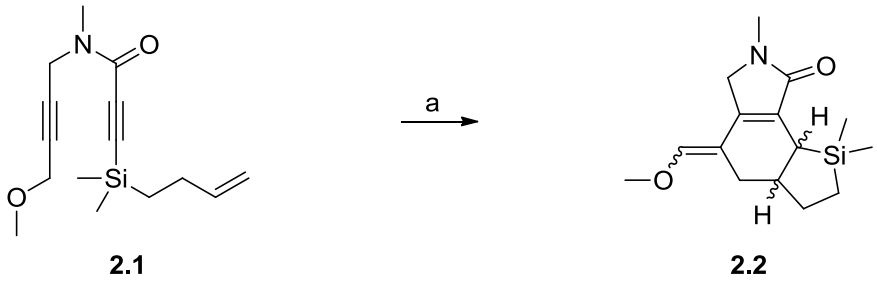
Entry	Base	Yield
1	Et_3N	46
2	Pyridine	38
3	DIPEA	55
4	2,6-Lutidine	71

Table 2.6: Different Bases Tested for Amide Coupling

The use of pyridine as a base afforded the required product in 38% yield, while *N*,*N*-diisopropylethylamine delivered a slight improvement over triethylamine. The highest yield was obtained with 2,6-lutidine (Entry 4, **Table 2.6**) which afforded the required amide **2.1** in 71% yield. A tendency is notable in **Table 2.6** suggesting that more sterically hindered bases give higher yields of desired amide **2.1**. At the beginning of this stage during the synthesis of coupling precursor **2.4** the but-3-en-1-yldimethylsilane group in **2.18** was removed by action of various reagents; a similar effect could be induced by unhindered nitrogen bases during the formation of amide **2.1**.

2.1.3. Thermal Cyclisation

Once cyclisation precursor **2.1** had been obtained, attempts at the cyclisation could proceed. Although there was experimental evidence to suggest the cascade would work, considering the amount of work that had already been required it was expected that this would necessitate a significant effort. To our delight the cascade was successful with the first attempt.

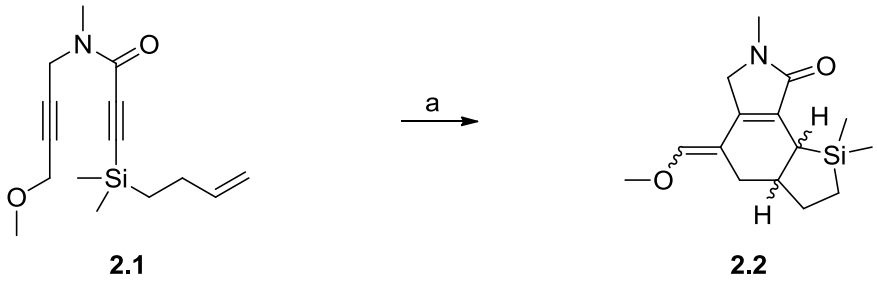


2.1 **2.2**

Reagent and Conditions: (a) Toluene, 0.1M, reflux, 12h, 30%.

Scheme 2.24: Thermal Cyclisation of Precursor **2.1** at 0.1M concentration

Unfortunately, the above thermolysis failed to give any isolable products in high yield. In order to test if the concentration of the starting material was a problem, heating of **2.1** in toluene was repeated at 0.01M.



2.1 **2.2**

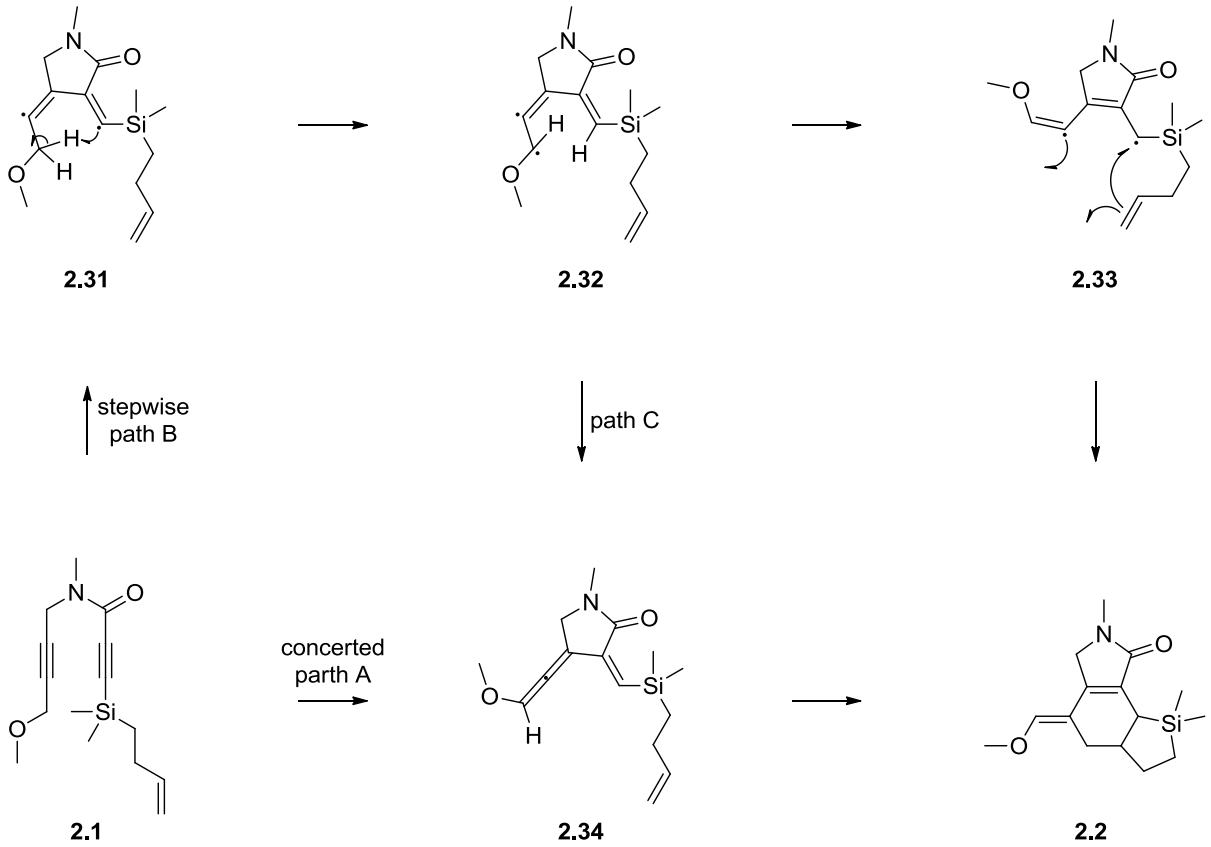
Reagent and Conditions: (a) Toluene, 0.01M, reflux, 16h, 38%.

Scheme 2.25: Thermal Cyclisation of Precursor **2.1** at 0.01M Concentration

After amide **2.1** was heated in toluene at reflux in 0.01M concentration of the starting material (to avoid polymerisation), tricycle **2.2** was generated in 38% yield. Although the reaction took a longer time to reach completion, the yield of cyclisation product increased up to 38%.

The reaction to form tricycle **2.2** was encouraging. The formation of a complex tricycle ring from a simple starting material, using no reagent other than solvent was remarkable. Indeed, extensive searching of the literature indicated that the reaction was unique; this was a new way of forming polycyclic structures as reported previously in our group.

As in the example shown in **Section 1.45**, the isolation of lactam **2.2** ruled out the previously proposed acid-catalysed mechanism as no bromine is present in the molecule to generate catalytic amounts of hydrogen bromide in solution.[144] Following these observations the mechanism in **Scheme 2.26** was proposed.



Scheme 2.26: Proposed Mechanism for the Formation of Tricycle **2.2**

In **Scheme 2.26** concerted path A would proceed by an intramolecular ene reaction to give the allene intermediate **2.34**, which could also result from the radical pathway B. Either a Diels-Alder reaction from allene **2.34** to lactam **2.2** could occur, or alternatively, the cycloaddition pathway from the bi-radical **2.33** would also result in the formation of the lactam **2.2**.[197]

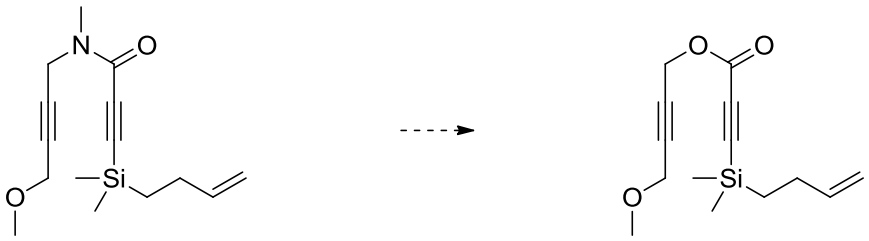
The difficulties associated with the amine and alcohol protection/deprotection and amide coupling for the synthesis of the cyclisation precursor **2.1** had been successfully solved. The

newly developed method has proven highly popular in the Parsons group and is currently employed in studies towards the total synthesis of the antibiotic Lactonamycin **1.164**. Furthermore, this method can potentially be used in the synthesis of other natural products (see **Chapter 3**).

2.2. Investigation through Modification of the Amide Linker

2.2.1. Outline of Investigation

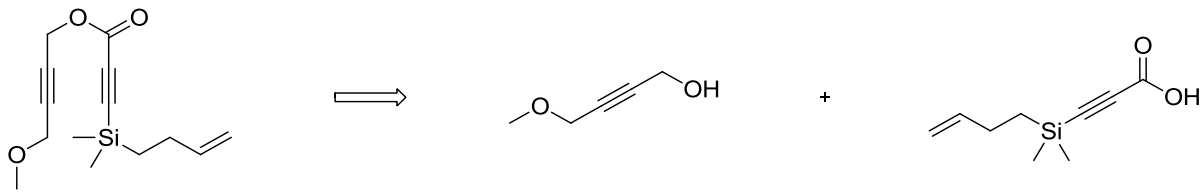
To enable us to further understand the importance of the amide linker in the cyclisation mechanism, we opted to exchange the amide for an ester linker (**Figure 2.1**).



2.1 **2.35**

Figure 2.1: Novel Cyclisation Precursor Consisting of an Ester Linker

An overview of our retrosynthetic plan is depicted in **Scheme 2.27**. In this analysis, cyclisation precursor **2.35** was disconnected at the ester linkage. This process leads to the previously synthesised (3-(but-3-en-1-yldimethylsilyl)propiolic acid) **2.4** and alcohol **2.38**.



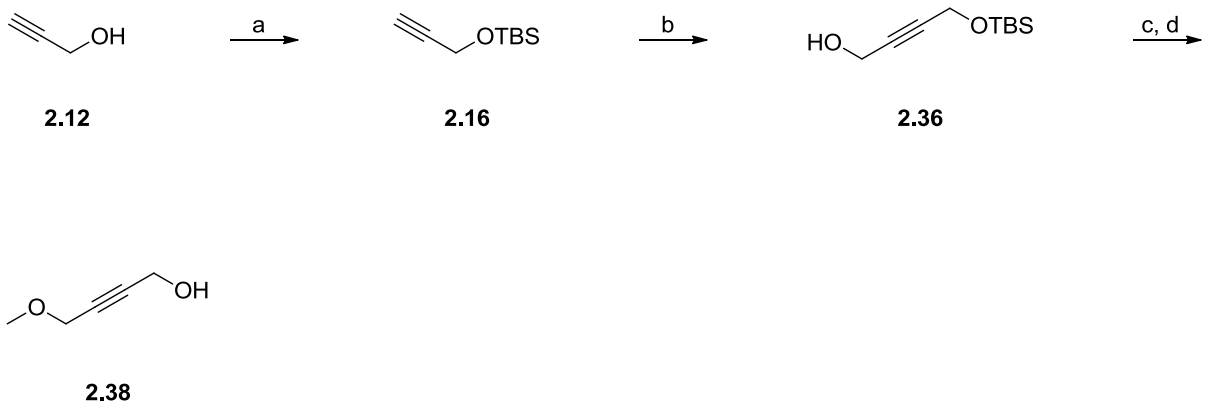
2.35 **2.38** **2.4**

Scheme 2.27: Retrosynthetic Analysis of Cyclisation Precursor **2.35**

2.2.2. Synthesis of Cyclisation Precursor 2.35

In conjunction with the efforts to form acid **2.4** and amine **2.3**, a synthesis of 4-methoxybut-2-yn-1-ol **2.38** was developed. Two routes to this intermediate were considered, these routes are illustrated in **Scheme 2.28** and **Scheme 2.29**.

Scheme 2.28 below illustrates the synthesis of desired material **2.38**.



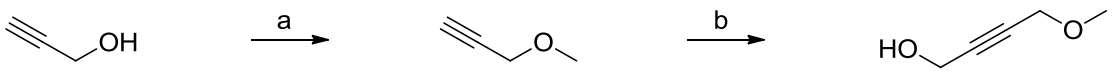
Reagent and Conditions: (a) *tert*-Butyldimethylsilyl chloride, imidazole, CH_2Cl_2, 0 °C to rt, 1h. 98%; (b) *n*-BuLi, THF then paraformaldehyde, -78 °C to rt, 16h, 82%; (c) KOH, MeI, DMSO, rt, 16h, 79%; (d) TBAF, THF, 0 °C to rt, 3h, 88%.

Scheme 2.28: Synthesis of 4-methoxybut-2-yn-1-ol **2.38**

The use of imidazole with *tert*-butyldimethylsilyl chloride in dichloromethane proved to be effective and resulted in the mild conversion of propargyl alcohol **2.12** to *tert*-butyldimethylsilyl ether **2.16** in excellent yield (98%).[166] The treatment of the silyl ether **2.16** with *n*-butyllithium in THF and the subsequent addition of parafomaldehyde at -78 °C afforded the desired alcohol **2.36** in 82% yield.[139] The treatment of the propargylic alcohol **2.36** with potassium hydroxide and subsequent reaction with methyl iodide in DMSO produced the required methyl ether in 70% yield.[157] The removal of the silyl protecting group with tetrabutylammonium fluoride (TBAF) in THF afforded the required alcohol **2.38** in 88% yield.[186]

A review of the literature revealed that although 4-methoxybut-2-yn-1-ol **2.38** was known, the syntheses that were developed were not ideal. Evidently, there was room for improvement; techniques to avoid a lengthy synthesis and to gain good reproducible yields

were necessary. In response to these issues, a useful process was quickly developed from standard chemistry (S**cheme 2.29**).



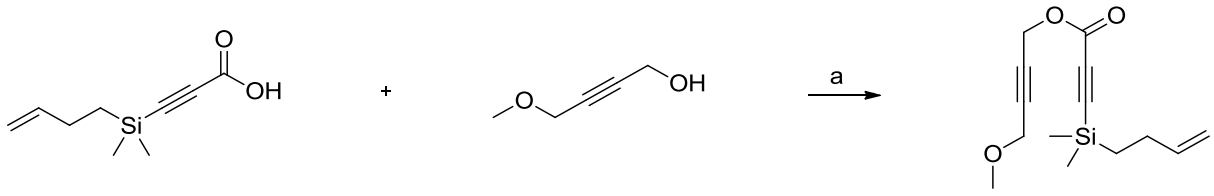
2.12 **2.37** **2.38**

Reagents and Conditions: (a) NaOH, H_2O, Me_2SO_4, 2h, 80%; (b) *n*-BuLi, THF then paraformaldehyde, -78 °C to rt, 16h, 86%.

Scheme 2.29: Synthesis of 4-methoxybut-2-yn-1-ol **2.38**

Treatment of a solution of propargyl alcohol **2.12** with aqueous sodium hydroxide followed by the addition of dimethyl sulfate afforded the methyl ether **2.37** in 80% yield.[198] It was observed that the yield was much lower than expected for a simple *O*-methylation, the volatility of the product was considered as a probable explanation. The treatment of the methyl ether **2.37** with *n*-butyllithium in THF and the subsequent addition of parafomaldehyde at -78 °C gave the desired alcohol **2.38** in 86% yield.[139] As the synthetic sequence was easier to perform and afforded a higher yield than the sequential route previously used, this was selected as the method of choice for making 4-methoxybut-2-yn-1-ol **2.38**.

The reaction of newly formed alcohol **2.38** with the acyl chloride derived from 3-(but-3-en-1-yldimethylsilyl)propiolic acid **2.4** in the presence of 2,6-lutidine as a base, yielded desired cyclisation precursor **2.35**.



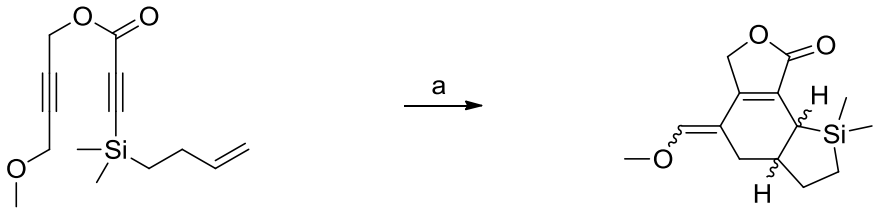
2.4 **2.38** **2.35**

Reagent and Conditions: (a) Oxalyl chloride, $DMF_{(cat.)}$, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 16h, 74%.

Scheme 2.30: Synthesis of Cyclisation Precursor **2.35**

2.2.3. Thermal Cyclisation

The newly formed cyclisation precursor **2.35** was heated in toluene, resulting in the clean cyclisation of 1,6-diyne **2.35** to form the tricycle **2.39**.

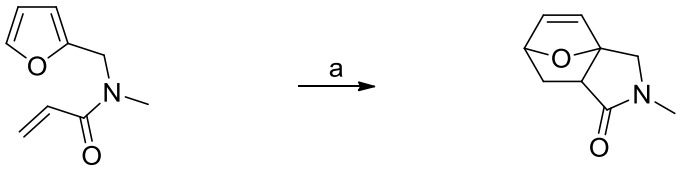


2.35 **2.39**

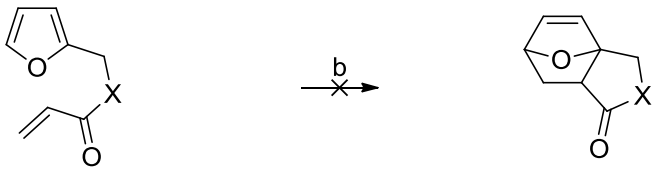
Reagent and Conditions: (a) Toluene, reflux, 0.01M, 20h, 40%

Scheme 2.31: Thermal Cyclisation of Precursor **2.39**

Interestingly, the ester linkage caused the rate of reaction to significantly decrease. A similar observation had previously been described by Parker *et al.*[199] during studies on the intramolecular Diels-Alder reaction of amides and esters. Parker and co-workers have demonstrated that some facile Diels-Alder reactions of tertiary amides **2.40** fail with the corresponding esters or secondary amides **2.42a-b** in place (**Scheme 2.32**). The author proposed that this was in account of a transoid relationship of the diene and dienophile across the ester moiety.



2.40 **2.41**



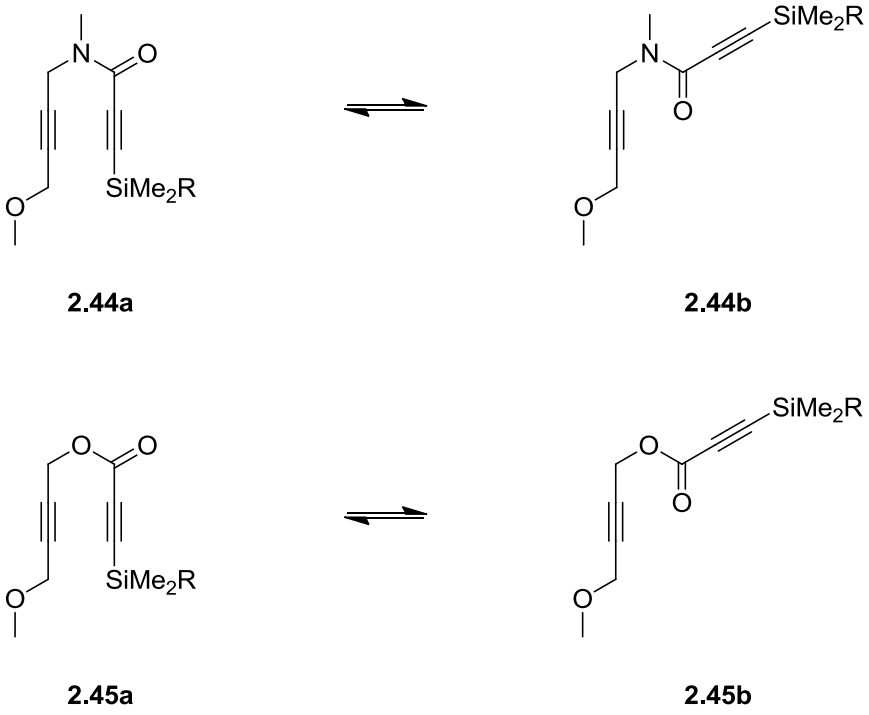
2.42a-b **2.43a-b**

2.42a: X = O, **2.42b**: X = NH

Reagents and Conditions: (a) Benzene, 80 °C, 6 days; (b) Benzene, 80 °C, 6 days.

Scheme 2.32: Amide/Ester Cyclisation Comparison

Our system could endure the same constraints, as illustrated in **Scheme 2.33**. The ester linker predominantly adopts a transoid relationship **2.45b** over the reactive cisoid diyne **2.45a**. During the process, the distance between the two alkynic bonds increases and a decrease in thermal reactivity is expected, this was indeed the case. The thermal cyclisation of compound **2.1** and **2.35** exhibited significant difference.



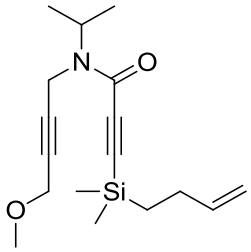
Scheme 2.33: Relationships of Resonance Forms

Following the assumption that the cyclisation was favoured by the cisoid conformation, it was anticipated that the attachment of a sterically demanding group on the nitrogen would enhance the cisoid geometry, displace the equilibrium to the left, decrease the distance between the two alkynic bonds and hence increase the rate of reaction. Therefore, the chosen course of action was to synthesise a novel cyclisation precursor consisting of a bulky *N*-substituted 1,6-diyne system.

2.3. Synthesise of a Novel Cyclisation Precursor Consisting of a Bulky *N*-Substituted 1,6-Diyne System

2.3.1. Outline of Investigation

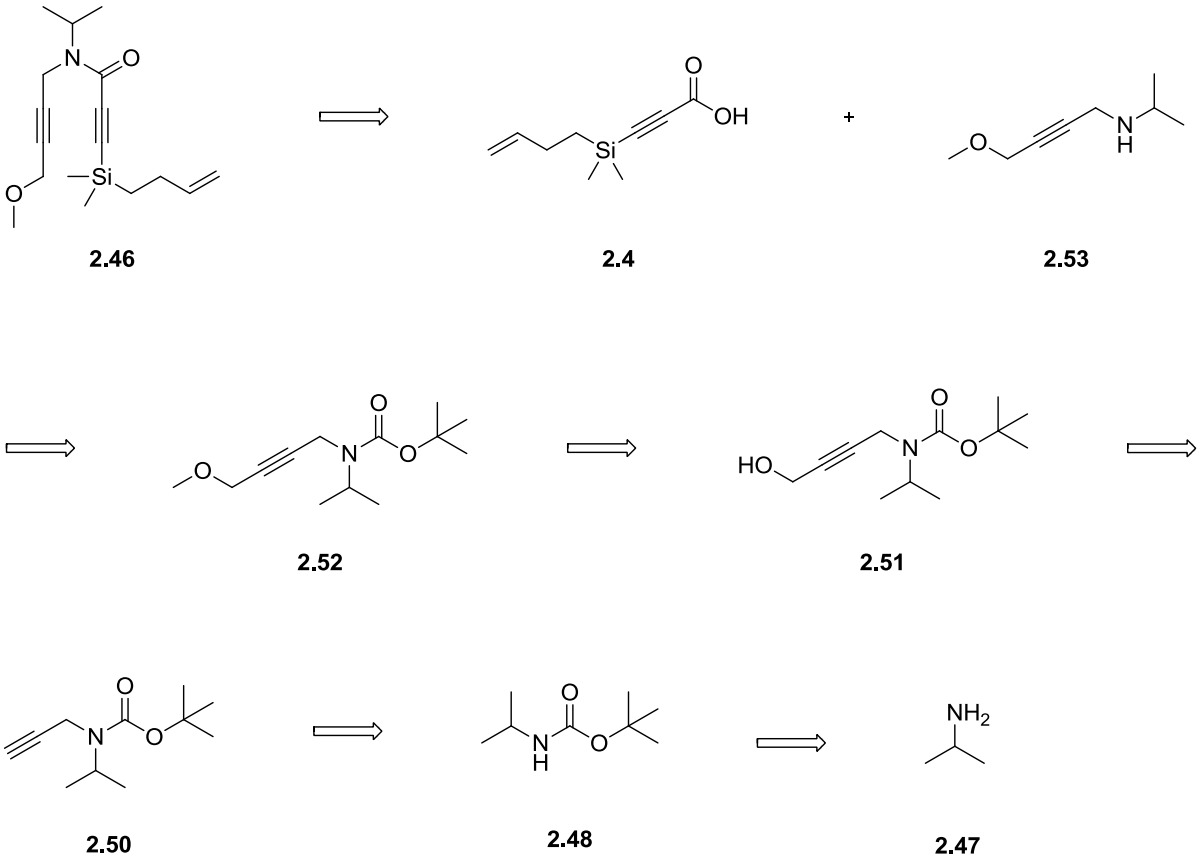
Due to the immediate availability of isopropylamine in the laboratory, amide **2.46** (**Figure 2.2**) was selected as a new synthetic target.



2.46

Figure 2.2: Novel Cyclisation Precursor **2.46**

The retrosynthetic approach for the cyclisation precursor **2.46** is depicted in **Scheme 2.34** below.



2.46 **2.4** **2.53**

2.52 **2.51**

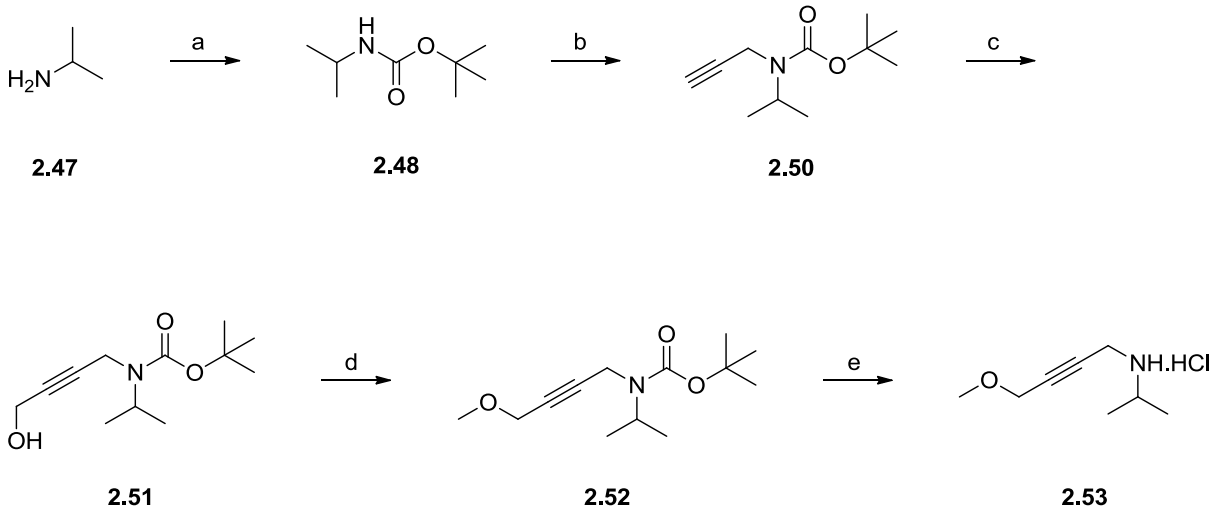
2.50 **2.48** **2.47**

Scheme 2.34: Retrosynthetic Analysis of Cyclisation Precursor **2.46**

A disconnection at the amide moiety leads to the previously synthesised (3-(but-3-en-1-yldimethylsilyl)propiolic acid) **2.4** and secondary amine **2.53**. The latter can be generated from protected amine **2.52**. In addition, compound **2.52** can be easily synthesised by deprotonation of the terminal alkyne in the *N*-Boc amine **2.50** and subsequent quenching with paraformaldehyde followed by Williamson ether synthesis. Reaction of secondary amine **2.48** and the propargyl bromide **2.49** can provide *N*-Boc amine **2.50**. Furthermore, amine **2.48** can be obtained from commercially available isopropylamine **2.47**.

2.3.2. Synthesis of the Cyclisation Precursor 2.46

Scheme 2.35 below illustrates the synthesis of desired material **2.53**.



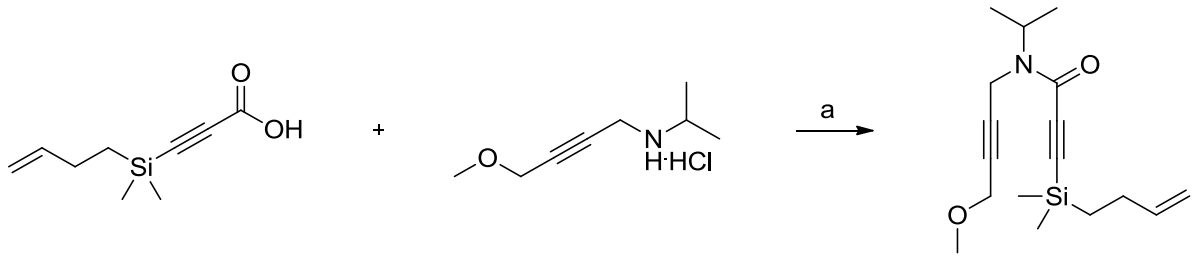
Reagents and Conditions: (a) Di-*tert*-butyl dicarbonate, DMAP, THF, 0 °C to rt, 16h, 71%; (b) NaH, propargyl bromide, DMF, 0 °C to rt, 16h, 66%. (c) *n*-BuLi, THF then paraformaldehyde, -78 °C to rt, 16h, 81%; (d) MeI, KOH, DMSO, rt, 16h, 86%; (e) 4M HCl, dioxane, 0 °C to rt, 4h, 74%.

Scheme 2.35: Synthesis of Amine **2.53**

Protection of commercially available isopropylamine **2.47** with di-*tert*-butyl dicarbonate in the presence of DMAP afforded the *tert*-butyl isopropylcarbamate **2.48** in 71% yield.[200] Propargylation of the protected amine **2.48** was carried out by using NaH, followed by propargyl bromide **2.49** addition (66%). The treatment of the *tert*-butyl-isopropyl(prop-2-yn-

1-yl)carbamate **2.50** with *n*-butyllithium in THF, followed by subsequent addition of paraformaldehyde at -78 °C afforded the desired alcohol **2.51** in 81% yield.[139] Treatment of the alcohol **2.51** with potassium hydroxide, followed by reaction with methyl iodide in DMSO, afforded the required methyl ether **2.52** in 86% yield.[157] The Boc group was cleanly removed from the compound **2.52** with 4M solution of hydrogen chloride in dioxane and the amine salt of the compound formed was used without further purification for the subsequent coupling reaction.[164]

The reaction of newly formed amine **2.53** with the acyl chloride derived from 3-(but-3-en-1-yldimethylsilyl) propiolic acid **2.4** in the presence of 2,6-lutidine as a base, yielded desired cyclisation precursor **2.46**.



2.4 **2.53** **2.46**

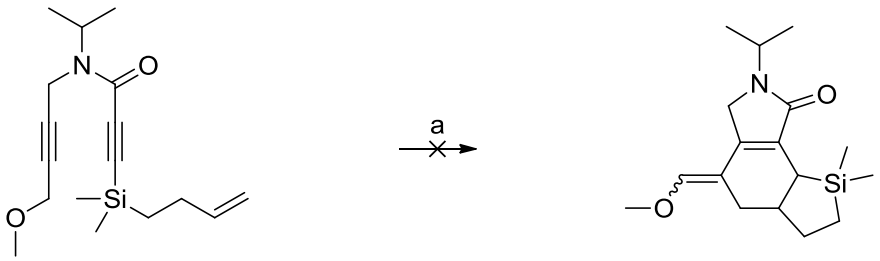
Reagent and Conditions: (a) Oxalyl chloride, $DMF_{(cat.)}$, 2,6-lutidine, CH_2Cl_2, 16h, 70%.

2,6-lutidine

Scheme 2.36: Synthesis of Cyclisation Precurs`or **2.46**

2.3.3. Thermolysis of 1,6-Diyne 2.46

The 1,6-diyne **2.46** was heated in toluene for 24 hours, yet it failed to give the tricyclic product **2.54** and the starting material was the only identifiable product isolated from the reaction mixture.

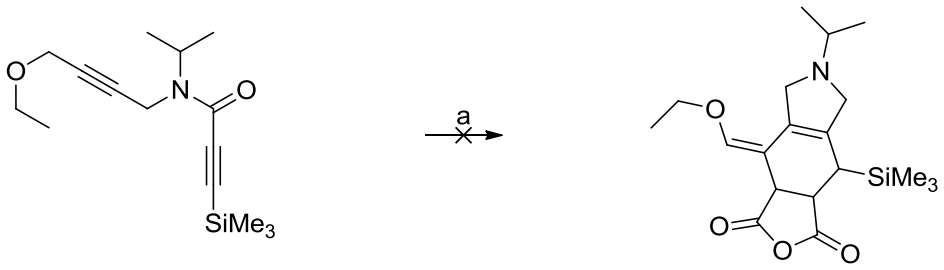


2.46 **2.54**

Reagent and Conditions: (a) Toluene, reflux, 0.01M, 24h.

Scheme 2.37: Thermolysis of **2.46** at 0.01M Concentration

In contrast to the *N*-methyl amide equivalent **2.1**, it was observed that cyclisation precursor **2.46** did not cyclise to form the tricyclic compound **2.54**. This replicated Oluwakemi's result as indicated in **Scheme 2.38** for a selected example.[201]

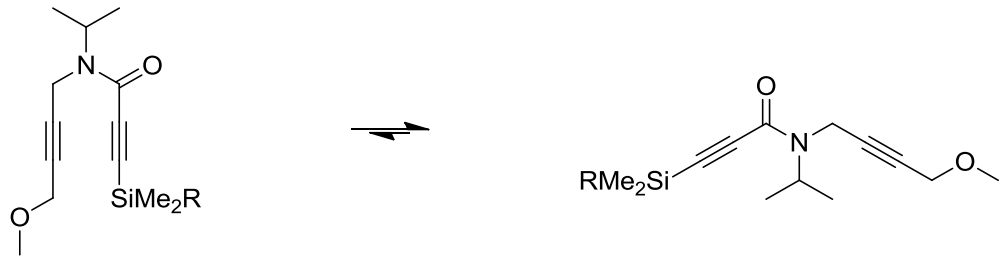


2.55 **2.56**

Reagents and Conditions: (a) Toluene, reflux, maleic anhydride, 0.1M, 32h.

Scheme 2.38: Work by Oluwakemi[201]

It can be concluded that the attachment of an isopropyl group on the nitrogen displaces the equilibrium to the right. It is safe to conclude that the sterically demanding isopropyl group on nitrogen have increased the distance between the two alkynic bonds and thereby decreased the rate of cyclisation reaction.



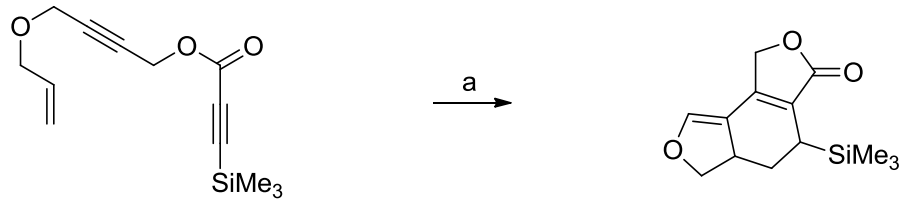
2.57a **2.57b**

Scheme 2.39: Relationships of Resonance Forms

2.4. Effects of Substituents on the Rate of Cyclisation

The rate enhancement resulting from the replacement of hydrogen atoms on the carbon tethering two reacting centres with alkyl substituents has been widely used in organic synthesis[202] and several of these examples will be discussed in this thesis.

The following work aimed to devise and execute a series of experiments with the intention of gaining a better understanding of the rate of the novel thermal cyclisation discovered by Parsons *et al.*[138,139] (**Scheme 2.40**).



2.58 **2.59**

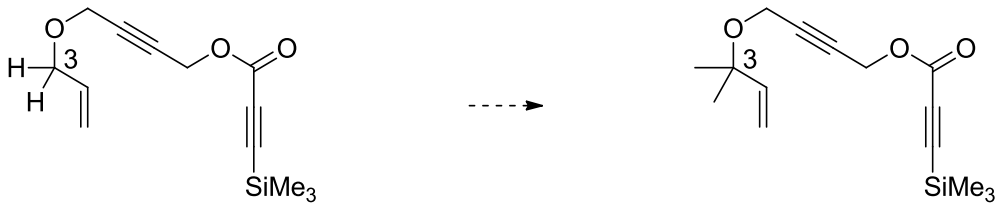
Reagents and Conditions: (a) Toluene, 0.1M, 13h, reflux, 85%

Scheme 2.40: Thermal Cyclisation of Precursor **2.58**

2.4.1. Replacement of the C3 Methylene Hydrogens with a gem-Dimethyl Group

2.4.1.1. *Outline of Investigation*

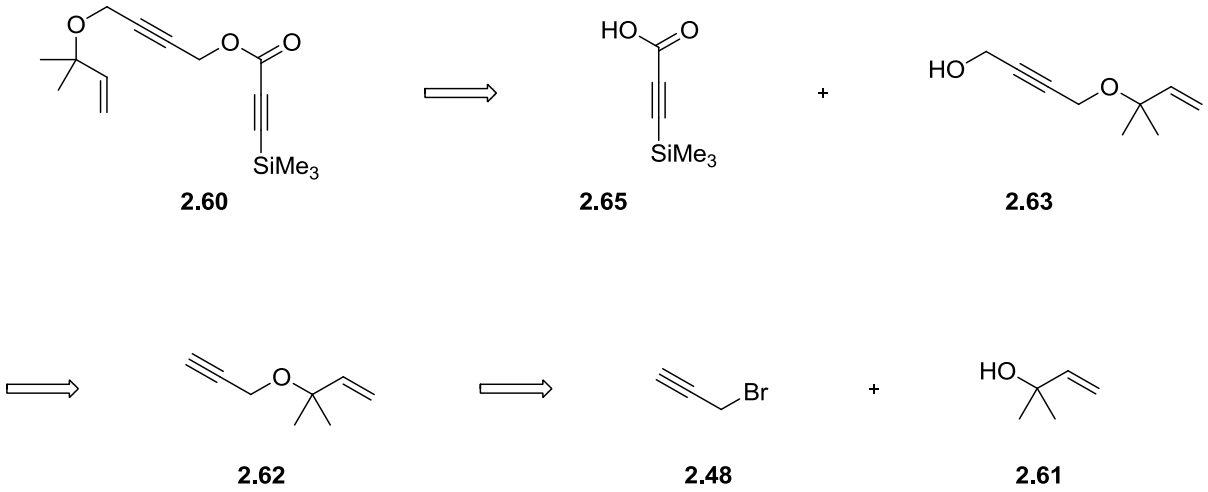
The introduction of a C-3 *gem*-dimethyl motif was introduced on **2.58** to favour the Thorpe-Ingold acceleration of the rate of cyclisation.



2.58 **2.60**

Figure 2.3: Novel Cyclisation Precursor **2.60**

The retrosynthetic approach for the cyclisation precursor **2.60** is depicted in **Scheme 2.41** below.



2.60 **2.65** **2.63**

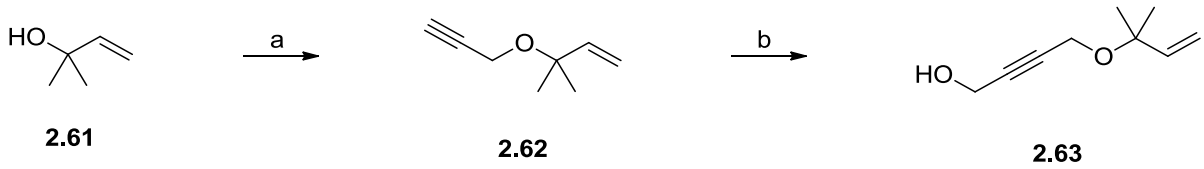
2.62 **2.48** **2.61**

Scheme 2.41: Retrosynthetic Analysis of Cyclisation Precursor **2.60**

A disconnection at the ester moiety leads to the commercially available (3-(trimethylsilyl)-2-propynoic acid) **2.65** and alcohol **2.63**. The latter can be easily synthesised by deprotonation of the terminal alkyne in the compound **2.62**, followed by subsequent quenching with paraformaldehyde. In addition, ether **2.62** could be accessed from alcohol **2.61** and propargyl bromide **2.49**, by employing Williamson's ether synthesis conditions.

2.4.1.2. *Synthesis of Cyclisation Precursor 2.60*

The construction of desired material **2.63** is detailed below in **Scheme 2.42**.



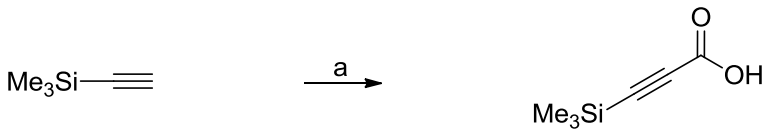
2.61 **2.62** **2.63**

Reagents and Conditions: (a) NaH, THF, propargyl bromide, 0 °C to rt, 16h, 65%; (b) *n*-BuLi, THF then paraformaldehyde, -78 °C to rt, 16h, 81%.

Scheme 2.42: Synthesis of Alcohol **2.63**

Deprotonation of the alcohol **2.61** with sodium hydride in THF, followed by the subsequent addition of propargyl bromide **2.49** at 0 °C afforded the desired ether **2.62** in 65% yield. Treatment of the 3-methyl-3-(prop-2-yn-1-yloxy)but-1-ene **2.62** with *n*-butyllithium in THF with the subsequent addition of paraformaldehyde at -78 °C afforded the desired alcohol **2.63** in 81% yield.[139]

The alkynic acid **2.65** could be prepared by deprotonation of trimethylsilyl acetylene **2.64** and quenching with CO_2, either as a gas[203] or a solid.[204] Deprotonation of trimethylsilyl acetylene was at first conducted using *n*-butyllithium. The use of this base generated pentanoic acid (also known as valeric acid). The preferred purification method for the reaction was distillation and the pentanoic acid impurity had a boiling point similar to that of the desired alkynoic acid **2.65**. A switch of base to methyllithium solved this problem and allowed synthesis of the desired acid in a typical yield of 78% from cheap starting materials and with no difference in yield when moving to large scale (typically performed on 0.1 to 0.2 mol).

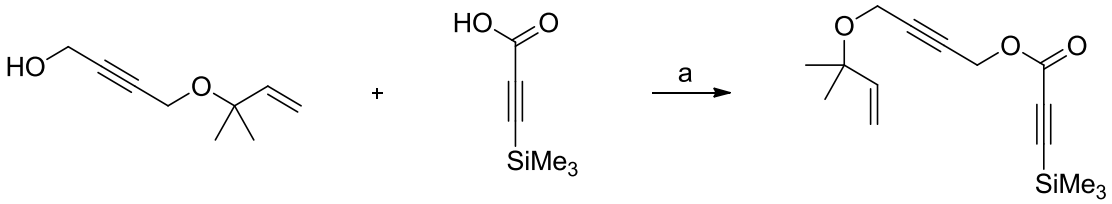


2.64 **2.65**

Reagents and Conditions: (a) MeLi, THF, -78 °C to -50 °C then $CO_{2(s)}$ then 1 M $HCl_{(aq)}$, 78%.

Scheme 2.43: Synthesis of (3-(trimethylsilyl)-2-propynoic acid) **2.65**

The reaction of alcohol **2.63** with the acyl chloride derived from 3-(trimethylsilyl)-2-propynoic acid **2.65** in the presence of 2,6-lutidine as a base, yielded desired cyclisation precursor **2.60**.



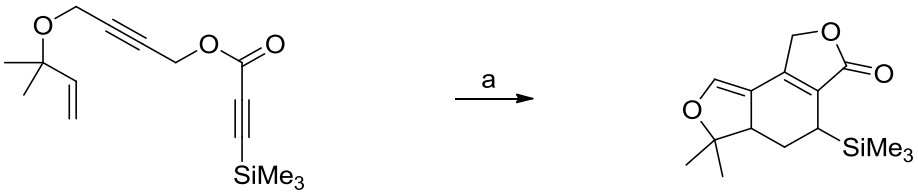
2.63 **2.65** **2.60**

Reagent and Conditions: (a) Oxalyl chloride, $DMF_{(cat.)}$, 2,6-lutidine, CH_2Cl_2, 16h, 74%.

Scheme 2.44: Synthesis of Cyclisation Precursor **2.60**

2.4.1.3. *Thermal Cyclisation*

The newly formed cyclisation precursor **2.60** was heated in toluene, resulting in the clean cyclisation of 1,6-diyne **2.60** to form the tricycle **2.66**.



2.60 **2.66**

Reagents and Conditions: (a) Toluene, 0.1M, reflux, 2h, 96%.

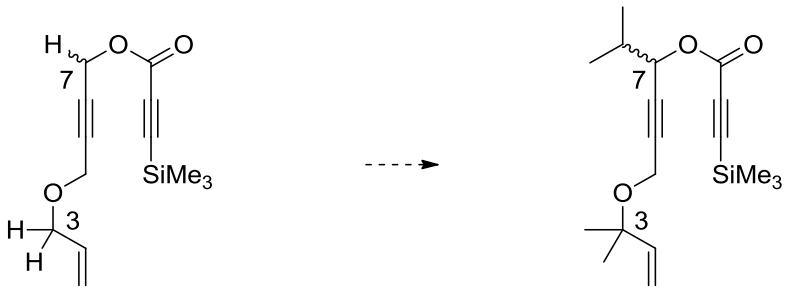
Scheme 2.45: Thermal Cyclisation of Precursor **2.60**

As predicted by the *gem*-dimethyl effect, replacement of the C3 methylene hydrogens of ester **2.58** with a dimethyl group produced an increase in the rate of cyclisation. As a result, the strain of the five-membered ring intermediate (and of the transition state leading to it) is relieved and the rate increased.

2.4.2. Replacement of the C7 Methylene Hydrogen with a Bulky Unit

2.4.2.1. *Outline of Investigation*

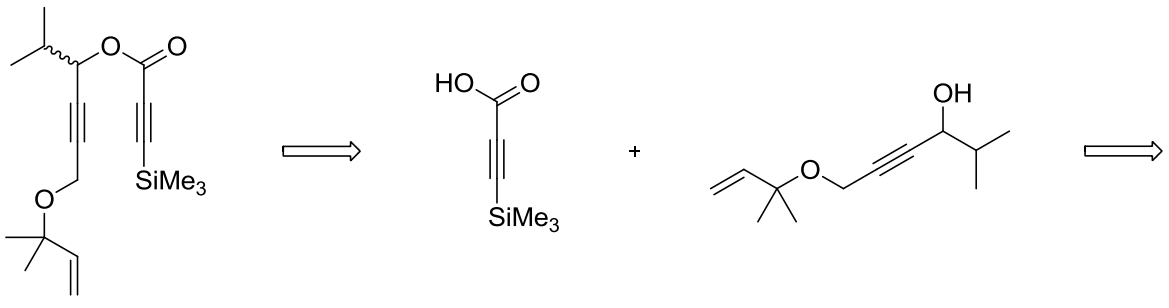
Replacement of the C7 methylene hydrogen in the ester **2.58** with a bulky unit should also produce an increase in the rate of cyclisation. It is noteworthy that the simultaneous replacement of the C3 methylene hydrogens with a *gem*-dimethyl group and C7 methylene hydrogen with sterically demanding isopropyl group of ester **2.58** should afford an accelerated increase in the rate of cyclisation.



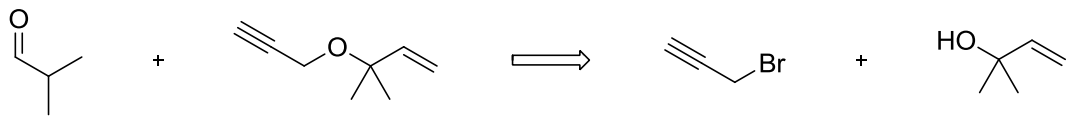
2.58 **2.67**

Figure 2.4: Novel Cyclisation Precursor **2.67**

The retrosynthetic approach for cyclisation precursor **2.67** is depicted in **Scheme 2.46** below.



2.67 **2.65** **2.69**



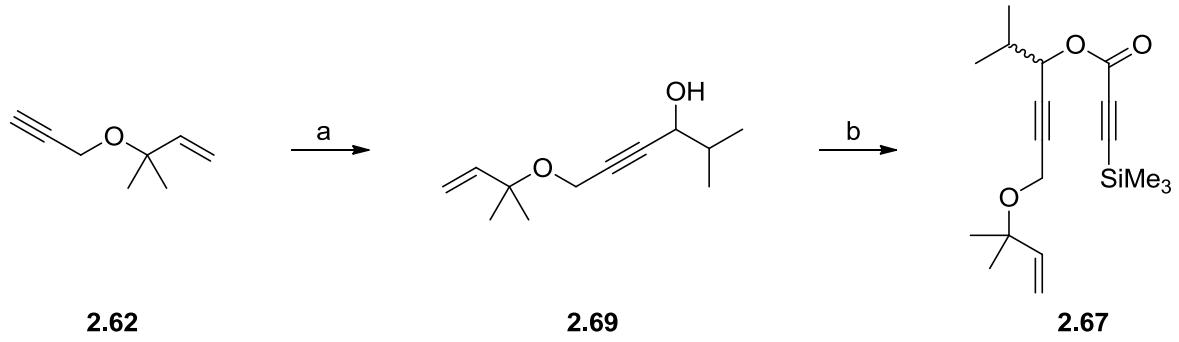
2.68 **2.62** **2.48** **2.61**

Scheme 2.46: Retrosynthetic Analysis of Cyclisation Precursor **2.67**

A disconnection at the ester moiety leads to the previously synthesised (3-(trimethylsilyl)-2-propynoic acid) **2.65** and secondary alcohol **2.69**. The latter could be generated from the alkylation of isobutyraldehyde **2.68** by the lithium salt of alkyne **2.62,** which could be accessed from alcohol **2.61** and propargyl bromide **2.49** by employing Williamson's ether synthesis conditions.

2.4.2.2. *Synthesis of Cyclisation Precursor 2.67*

Scheme 2.47 below illustrates the synthesis of desired material **2.67**.



2.62 **2.69** **2.67**

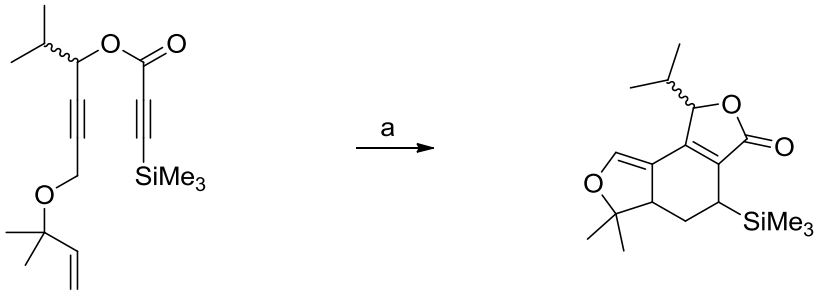
Reagents and Conditions: (a) *n*-BuLi, THF then isobutyraldehyde **2.68**, -78 °C to rt, 16h, 96%; (b) Oxalyl chloride, 3-(trimethylsilyl)-2-propynoic acid **2.65**, $DMF_{(cat.)}$, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 16h, 74%.

Scheme 2.47: Synthesis of Cyclisation Precursor **2.67**

Deprotonation at the terminal acetylene of compound **2.62** and alkylation with a slight excess of isobutyraldehyde proceeded in 96% yield. After quenching with saturated aqueous ammonium chloride solution and washing with saturated aqueous sodium bisulfate to remove excess aldehyde *via* its bisulfate adduct, the product **2.69** was found to be adequately pure.[205] The reaction of alcohol **2.69** with the acyl chloride derived from 3-(trimethylsilyl)-2-propynoic acid **2.65** in the presence of 2,6-lutidine as a base, yielded desired cyclisation precursor **2.67.**

2.4.2.3. *Thermal Cyclisation*

The newly formed cyclisation precursor **2.67** was heated in toluene, resulting in the clean cyclisation of 1,6-diyne **2.67** to form the tricycle **2.70**.



2.67 **2.70**

Reagents and Conditions: (a) Toluene, 0.1M, reflux, 30 min., 95%.

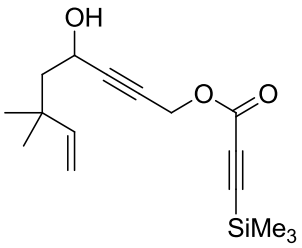
Scheme 2.48: Thermal Cyclisation of Precursor **2.70**

The cyclisation of ester **2.60** has been studied previously in order to assess the effect of methyl groups on rates. The study was extended to include isopropyl group and the reaction studied appeared to show a direct conversion into the corresponding cyclisation product (TLC analysis and visualization under the UV light indicated the completion of the cyclisation reaction after 30 min.). In this case, the relatively short time taken for the completion of the cyclisation reaction is an indication of the positive effect of the sterically demanding group on the geometry of the molecule. In principle, this could have resulted from the sterically demanding isopropyl group favouring the cisoid geometry, bringing the two alkynic bonds into closer proximity thereby increasing the rate of cyclisation reaction. This may have been aided by the methyl group on C3 and it is assumed that the mechanism would be identical to that of compound **2.1** (**Scheme 2.26**).

2.5. Synthesis of a New Cyclisation Precursor

2.5.1. Outline of Investigation

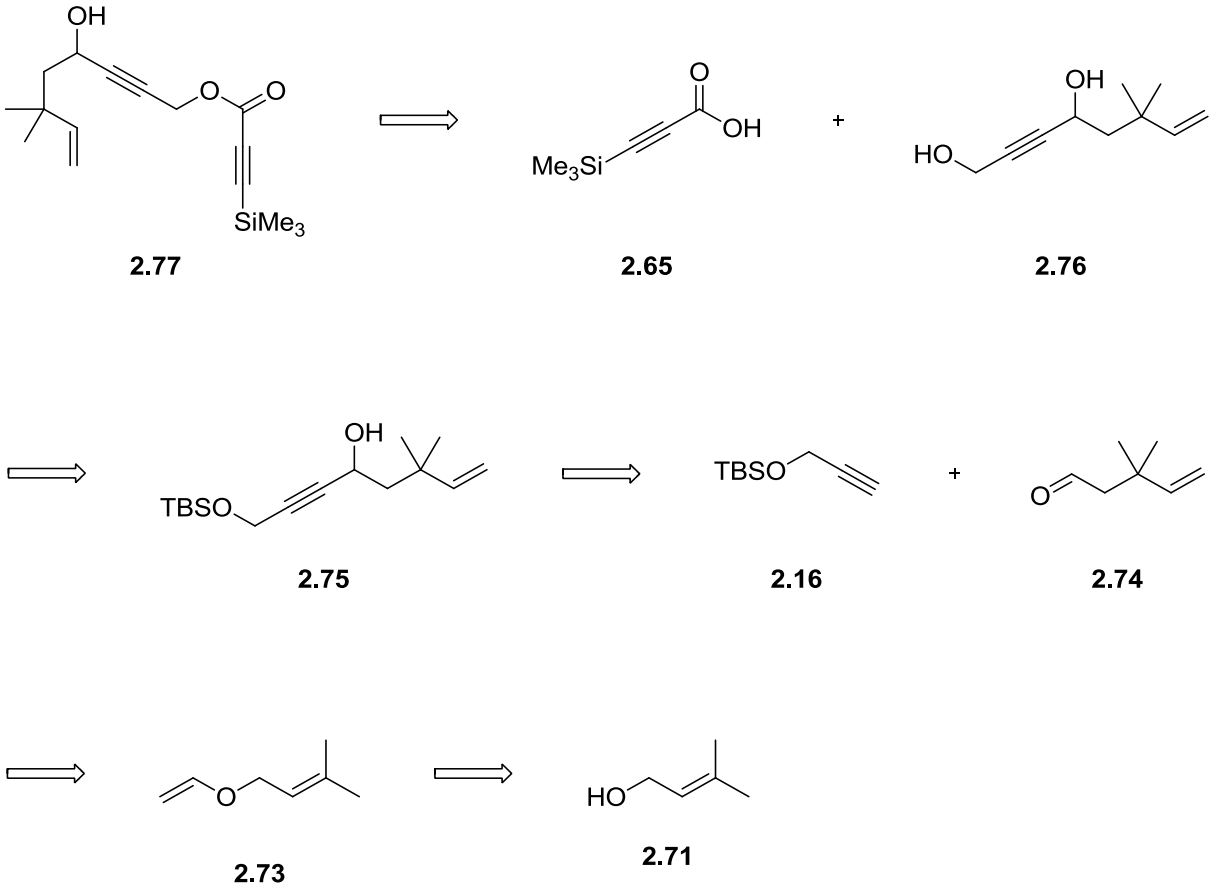
In order to further investigate the cyclisation, the ester **2.77** was chosen as a new synthetic target.



2.77

Figure 2.5: Novel Cyclisation Precursor **2.77**

The retrosynthetic approach for cyclisation precursor **2.77** is depicted in **Scheme 2.49**.



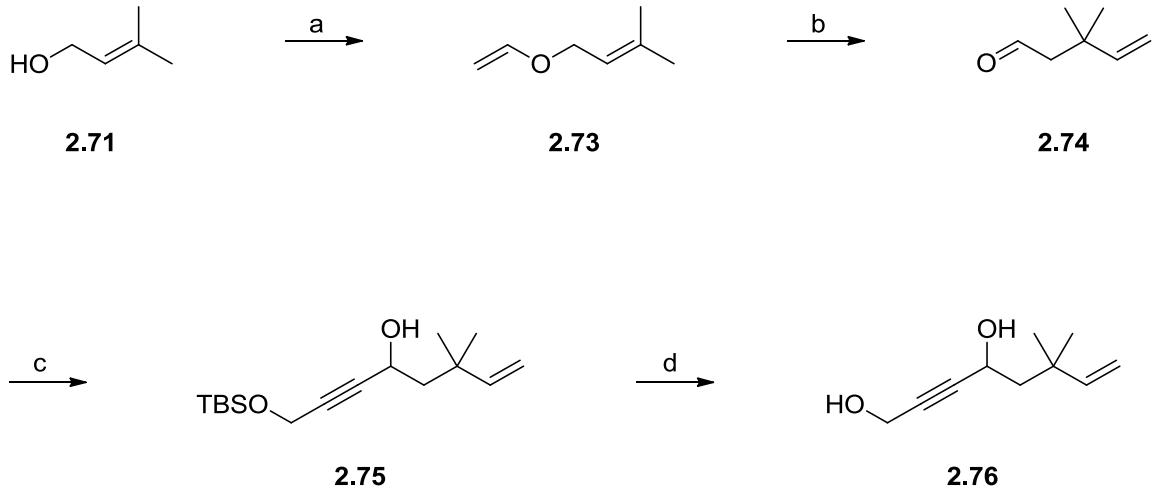
Scheme 2.49: Retrosynthetic Analysis of Cyclisation Precursor **2.77**

A disconnection at the ester moiety leads to the previously synthesised (3-(trimethylsilyl)-2-propynoic acid) **2.65** and alcohol **2.76**. The latter can be generated from protected alcohol **2.75**, which can be obtained from the alkylation of aldehyde **2.74** by the lithium salt of silyl-protected propargyl alcohol **2.16**. In addition, aldehyde **2.74** can be generated by simply

refluxing the vinyl ether **2.73**, which can be accessed from alcohol **2.71** and ethyl vinyl ether **2.72**.

2.5.2. Synthesis of Cyclisation Precursor 2.77

Scheme 2.50 below illustrates the synthesis of desired material **2.76**



2.71 **2.73** **2.74**

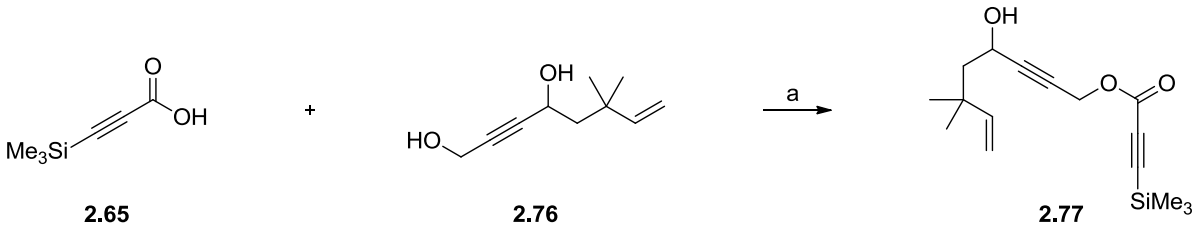
2.75 **2.76**

Reagents and Conditions: (a) $Hg(OAc)_2$, ethyl vinyl ether, 2 days, 66%; (b) Reflux, 24h, 97%; (c) *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane **2.16**, *n*-BuLi, THF, -78 °C to rt, 93%; (d) TBAF, THF, 2h, 95%

Scheme 2.50: Synthesis of Desired Alcohol **2.76**

The synthesis commenced with the formation of vinyl ether **2.73** from 3-methyl-2-buten-ol **2.71**. This reaction was carried out using mercuric acetate and ethyl vinyl ether **2.72** and desired vinyl ether **2.73** was obtained in 66% yield.[206] The 3-methyl-1-(vinyloxy)but-2-ene **2.73** was then heated at reflux for 24 hours and cooled to room temperature to obtain the title aldehyde **2.74** in excellent yield (97%).[219] Deprotonation at the terminal acetylene of silyl-protected alcohol **2.16** and alkylation with a slight excess of 3,3-dimethylpent-4-enal **2.74** proceeded in 93% yield.[205] Silyl deprotection of **2.75** was achieved using TBAF in THF.[186] A basic work-up provided desired alcohol **2.76** as a yellow, pure oil in 95% yield.

The reaction of alcohol **2.76** with the acyl chloride derived from 3-(trimethylsilyl)-2 propynoic acid **2.65** in the presence of 2,6-lutidine as a base, yielded desired cyclisation precursor **2.77**.



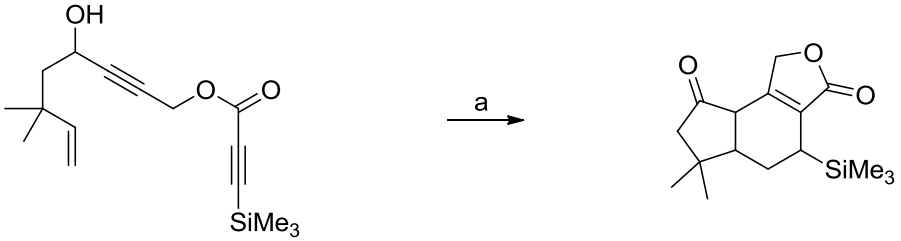
2.65 **2.76** **2.77**

Reagent and Conditions: (a) Oxalyl chloride, $DMF_{(cat.)}$, 2,6-lutidine, CH_2Cl_2, 16h, 70%.

Scheme 2.51: Synthesis of Cyclisation Precursor **2.77**

2.5.3. Thermal Cyclisation

The 1,6-diyne **2.77** was heated in toluene for 12 hours, resulting in total consumption of the starting material to give the tricyclic product **2.78** as the only identifiable product in a 82% yield. NMR, IR and mass analysis of the solid obtained revealed its structure to be ketone **2.78** below.



2.77 **2.78**

Reagents and Conditions: (a) Toluene, 0.01M, reflux, 12h, 82%**.**

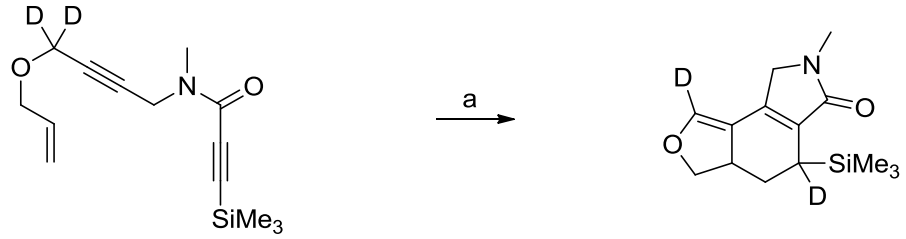
Scheme 2.52: Thermal Cyclisation of Precursor **2.77**

Tricycle **2.78** proved to be a solid only marginally soluble in diethyl ether; therefore the reaction solution only needed to be cooled, the precipitate collected through vacuum filtration and washed with a cold diethyl ether to produce the reasonable yield (82%).

2.6. Ketone Modification - Novel Synthesis of Furan-2(*5H*)-one

2.6.1. Outline of Investigation

Deuterium-labelling studies have previously confirmed that during the cyclisation discovered by Parsons *et al.*,[138,139] a hydrogen atom is abstracted intramolecularly (**Scheme 2.53**).

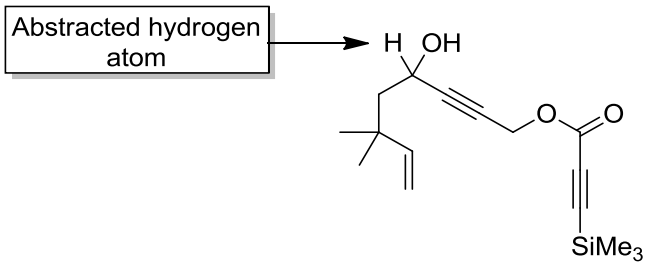


2.79 **2.80**

Reagents and Conditions: (a) Toluene, reflux, 16h, 90%.

Scheme 2.53: Cyclisation of Deuterated Compound **2.79**

A way to drastically alter the reactivity of compound **2.77** is to completely remove this hydrogen atom by oxidising the secondary alcohol moiety to a ketone (**Figure 2.6**).

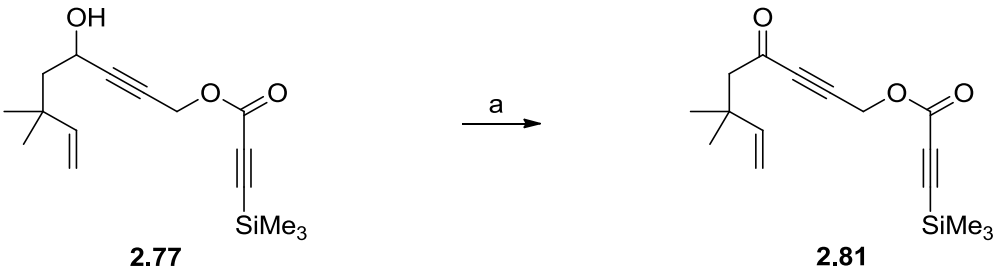


2.77

Figure 2.6: Position of the Abstracted Hydrogen Atom in **2.77**

2.6.2. Oxidation of Secondary Alcohol to Ketone

There are countless procedures available in the literature to oxidise secondary alcohols to ketones.[207] Inspiration came from the work of Jones *et al.*[208] on the oxidation of acetylenic alcohols employing chromic acid, generated from chromium(VI) trioxide and concentrated sulfuric acid. Preparation of Jones' reagent was achieved using a published procedure.[209]



2.77 **2.81**

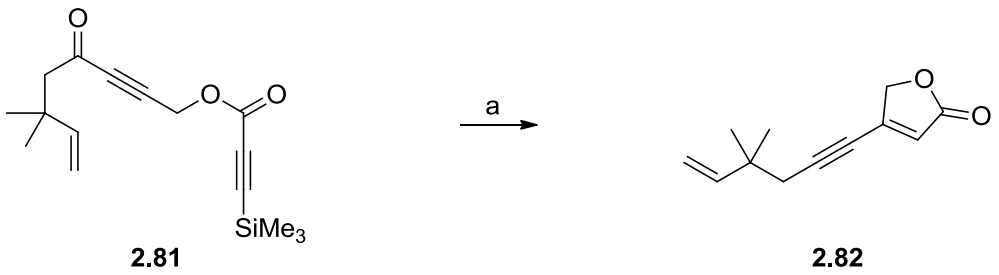
Reagents and Conditions: (a) 3.0M Jones' reagent, acetone, rt, 96%.

Scheme 2.54: Jones' Oxidation of **2.77**

Oxidation of alcohol **2.77** with this solution proceeded in 96% yield (**Scheme 2.54**). Further advantages to the use of this procedure include short reaction times and straight forward work-up conditions. Frequently, it was observed that only a simple filtration *via* a short column of silica was all that was required to acquire pure **2.81**.

2.6.3. Thermal Cyclisation

The next step was to test the thermolysis of **2.81** in refluxing anhydrous, degassed toluene. Identical to previous cyclisations a 0.01M concentration of the starting material was chosen.



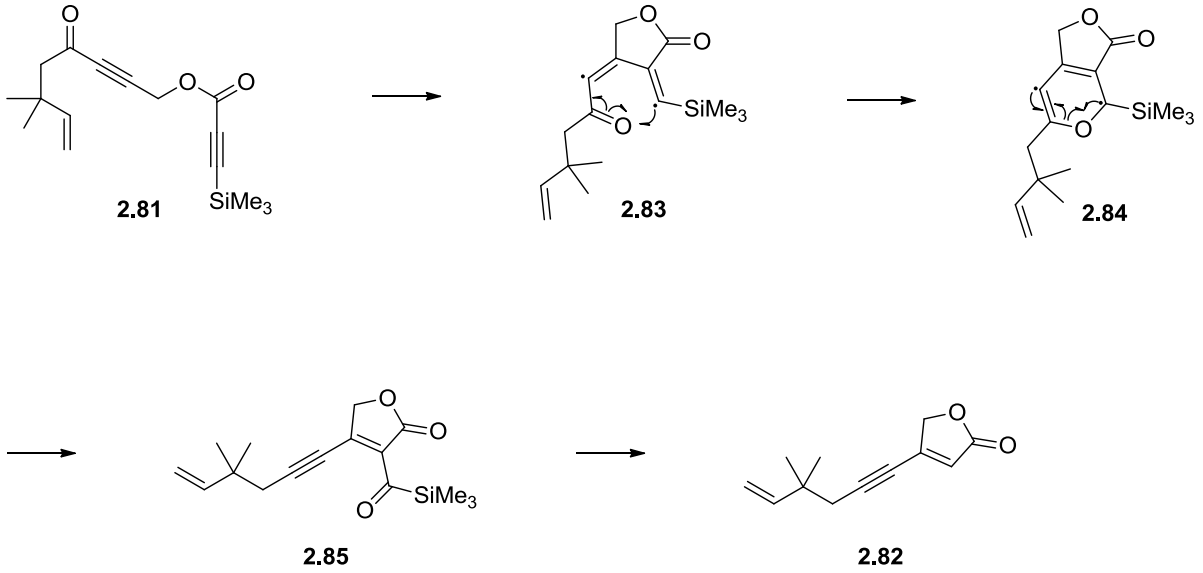
2.81 **2.82**

Reagents and Conditions: (a) Toluene, 0.01M, reflux, 6h, 30%.

Scheme 2.55: Thermal Cyclisation of Precursor **2.81**

When the ketone **2.81** was heated in toluene solution for 6 hours under reflux a remarkable transformation was observed; the alkyne **2.82** was isolated in 30% isolated yield (**Scheme 2.55**).

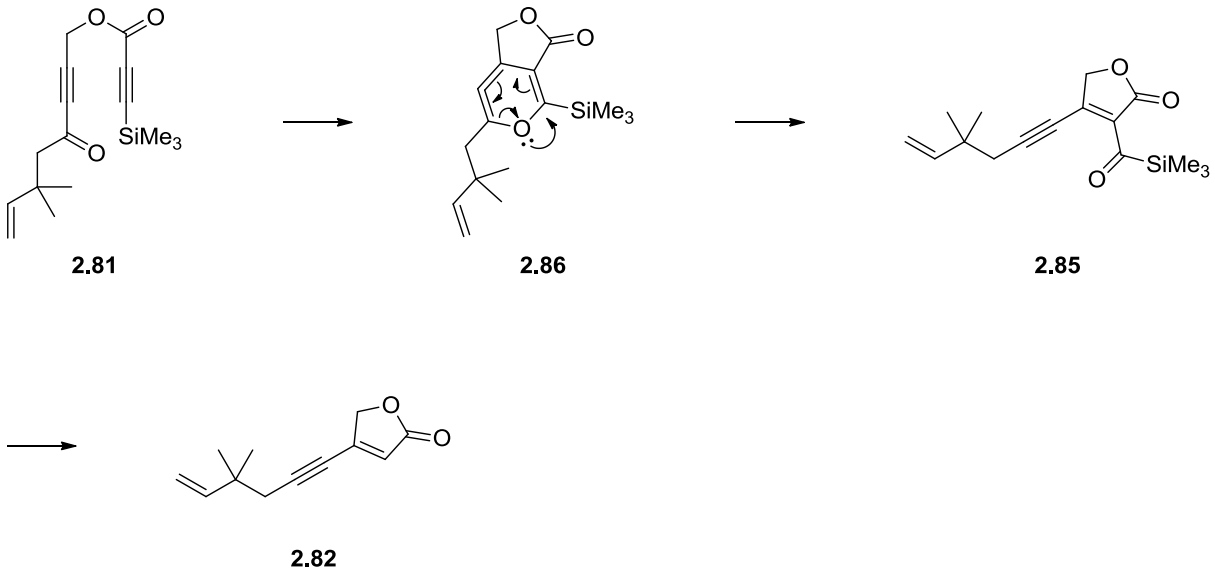
The formation of the alkyne **2.82** was totally unexpected and the mechanism outlined in **Scheme 2.56** was proposed to account for this transformation.



Scheme 2.56: Proposed Mechanism for the Formation of **2.82**

The bi-radical **2.83** could be formed as described in **Scheme 2.26** and instead of hydrogen atom abstraction, the alkenyl radical could add to the carbonyl group as illustrated in structure **2.83** to form the new bi-radical **2.84**. The fragmentation of **2.84** would give the acyl silane **285**, which on loss of carbon monoxide and benzyltrimethylsilane would give the observed product **2.82**.

A second mechanism based on the reported intramolecular [4+2] cycloaddition of conjugated *ynones*[210] was also proposed (**Scheme 2.57**).



2.81 **2.86** **2.85**

2.82

Scheme 2.57: Postulated *ynone* [4+2] Mechanism for the Formation of **2.82**

A concerted [4+2] cycloaddition between the ynone functionality and the silyl acetylene in **2.81** would yield highly strained heterocyclic allene **2.86**. Electrocyclic ring opening in **2.86** would yield the acyl silane **2.85** which on loss of carbon monoxide and benzyltrimethylsilane would give the observed product **2.82**.

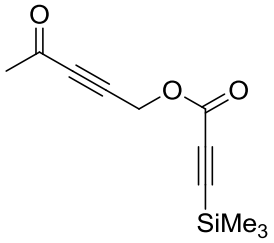
Unfortunately, no definitive empirical evidence for either mechanism is available and the question of which of these mechanisms is involved in the generation of compound **2.82** remains unanswered.

Since it was now obvious that the terminal alkene was not necessary for the cyclisation to occur (**Scheme 2.56** and **Scheme 2.57**), the chosen course of action was to synthesise a novel cyclisation precursor consisting solely of a diynone system.

2.7. Synthesis of a Novel Cyclisation Precursor Consisting Solely of a Diynone System

2.7.1. Outline of Investigation

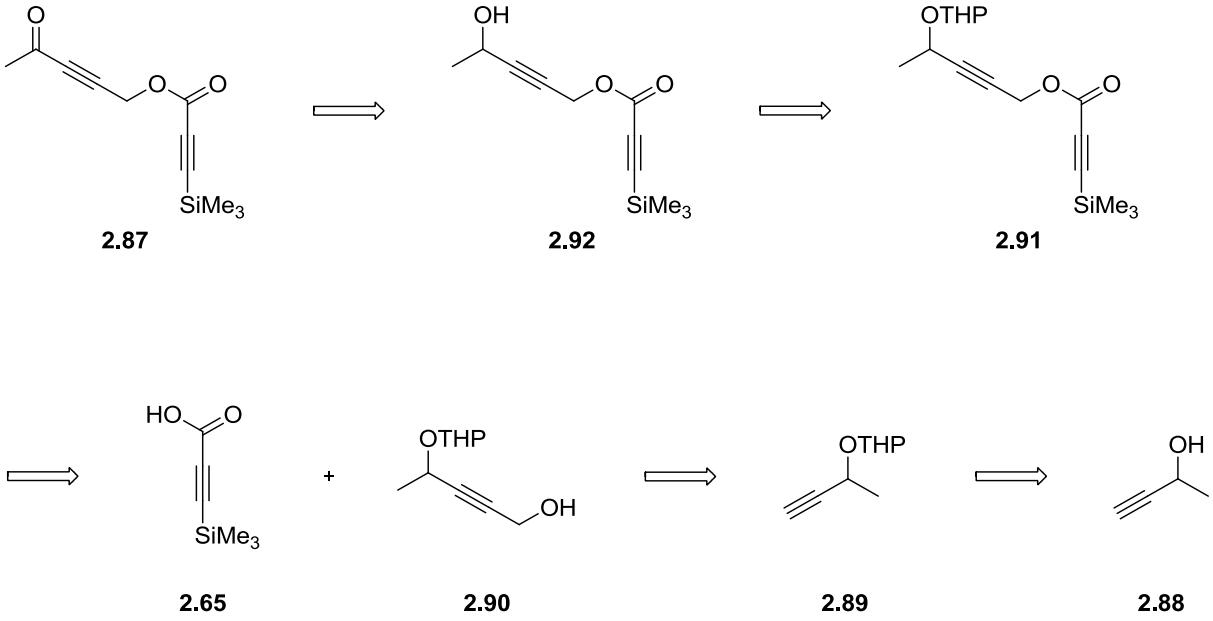
The novel cyclisation precursor **2.87** was selected in order to test the repeatability of the devised transformation (**Scheme 2.55**).



2.87

Figure 2.7: Novel Cyclisation Precursor **2.87**

The retrosynthetic approach envisaged for the cyclisation precursor **2.87** is shown in **Scheme 2.58** below.

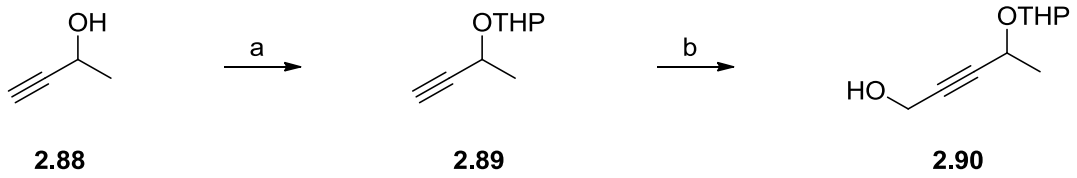


Scheme 2.58: Retrosynthetic Analysis of Cyclisation Precursor **2.87**

Ketone **2.87** can be generated from oxidation of the secondary alcohol **2.92**, which can be obtained from the elaboration of protected alcohol **2.91**. A disconnection at the ester moiety in **2.91** leads to the previously synthesised (3-(trimethylsilyl)-2-propynoic acid) **2.65** and alcohol **2.90**. The latter can be easily synthesised by deprotonation of the terminal alkyne in **2.89** and subsequent quenching with paraformaldehyde. Furthermore, compound **2.89** can be obtained from commercially available but-3-yn-2-ol **2.88**.

2.7.2. Synthesis of Cyclisation Precursor 2.87

Scheme 2.59 below illustrates the synthesis of desired material **2.90**



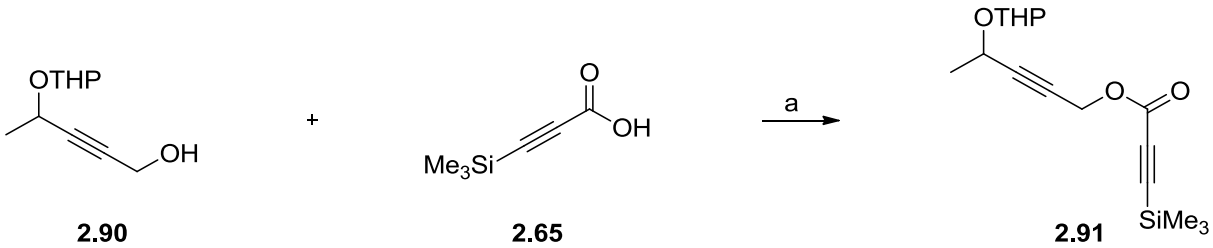
2.88 **2.89** **2.90**

Reagents and Conditions: (a) 3,4-dihydro-*2H*-pyran, *para*-toluenesulphonic acid, CH_2Cl_2, 0 °C to rt, 4h, 97%; (b) *n*-BuLi, THF then paraformaldehyde, -78 °C to rt, 16h, 83%.

Scheme 2.59: Synthesis of Alcohol **2.90**

But-3-yn-2-ol **2.88** was protected in near quantitative yield as its tetrahydropyranyl ether using 3,4-dihydro-*2H*-pyran in the presence of catalytic amount of *para*-toluenesulphonic acid.[211] Deprotonation of **2.89** was performed by the addition of one equivalent of *n*-butyllithium solution at -78 °C. Warming to -20 °C to ensure complete proton abstraction and reaction of the resulting lithium salt with excess paraformaldehyde followed by quenching with saturated aqueous NH_4Cl afforded desired alcohol **2.90**.[139]

The reaction of alcohol **2.90** with the acyl chloride derived from 3-(trimethylsilyl)-2-propynoic acid **2.65** in the presence of 2,6-lutidine as a base, yielded desired ester **2.91** in 82% yield.

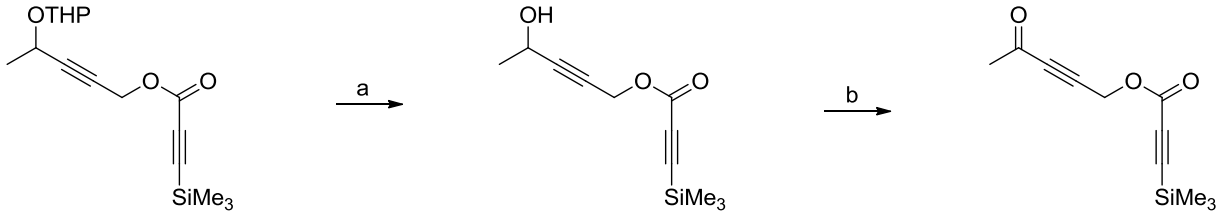


2.90 **2.65** **2.91**

Reagent and Conditions: (a) Oxalyl chloride, $DMF_{(cat.)}$, 2,6-lutidine, CH_2Cl_2, 16h, 82%.

Scheme 2.60: Synthesis of Ester **2.91**

Once the protection was no longer needed, the THP group was removed with catalytic amount of PPTS in MeOH (78%).[193] The oxidation of the secondary alcohol was performed in CH_2Cl_2 using DMP at room temperature and reached completion within 2 hours.[212]

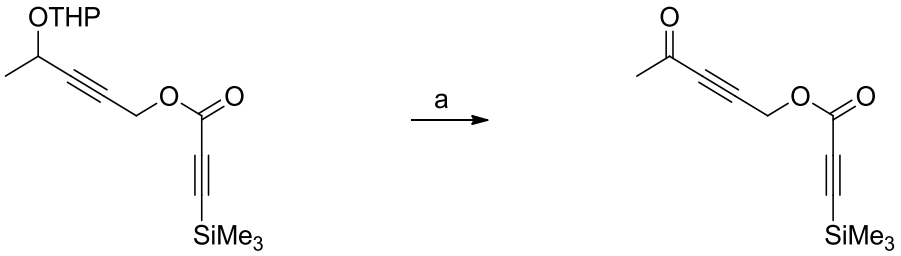


2.91 **2.92** **2.87**

(a) PPTS, MeOH, 45 °C to rt, 6h, 78%; (b) DMP, CH_2Cl_2, 0 °C to rt, 2h, 83%.

Scheme 2.61: Synthesis of Cyclisation Precursor **2.87**

The THP ether can be converted directly to an aldehyde or ketone using a variety of oxidative methods.[213] In most of the examples, the reagent cleaves the THP ether and then oxidises the alcohol to the carbonyl derivatives. There are countless procedures available in the literature to oxidise THP protected alcohols to ketones.[213] Inspiration came from our previous work on the oxidation of THP protected acetylenic alcohol employing chromic acid, generated from chromium(VI) trioxide and concentrated sulfuric acid.[208]



2.91 **2.87**

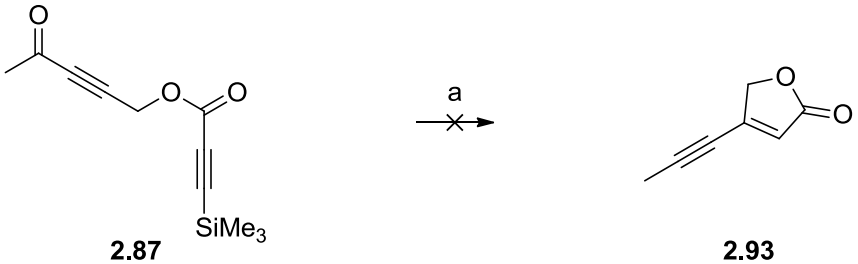
Reagents and Conditions: (a) 3.0M Jones' reagent, acetone, rt, 3h, 92%.

Scheme 2.62: Jones' Oxidation of **2.91**

Oxidative deprotection of THP ether **2.91** with this solution proceeded in very high yield. Added advantages to the use of this procedure are short reaction times and easy work-up conditions. Often it was found that only a simple filtration through a short column of silica was all that was required to obtain pure ketone **2.87**.

2.7.3. Thermolysis of Diynone 2.87

Heating the newly formed cyclisation precursor **2.87** in anhydrous, degassed toluene at 0.01M concentration for 24 hours resulted in the quantitative recovery of starting material **2.87**, with no sign of conversion to the cyclised product **2.93** or decomposition to any by-products.



Reagents and Conditions: (a) Toluene, 0.01M, reflux, 24h.

Scheme 2.63: Attempted Cyclisation of **2.87** in Refluxing Toluene

The presence of 2,2-dimethylbut-3-en-1-yl group in the molecule appears to be of fundamental importance for the cyclisation to proceed. Early work on the synthesis and examination of enediyne fragments reinforced a relationship between the critical inter-nuclear distance of the forming carbon-carbon bond and the cyclisation barrier.[77,78]

cd = 3.35 Å

Stable at room temperature

2.94

cd = 3.16 Å

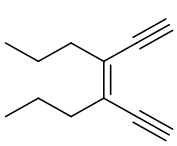
Spontaneous cyclisation

2.95

Scheme 2.64: Calculated *cd* Distance: Effect on the Bergman Cyclisation.

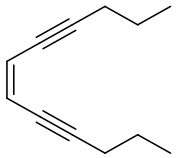
It could be then postulated that in cyclisation precursors containing a 2,2-dimethylbut-3-en-1-yl group, the approach of the two acetylene moieties is facilitated by resonance an effect which would not be observed for the methyl analogue (**Scheme 2.63**).

Moreover, there have been studies carried out on derivatives with increased cyclisation barriers; the large activation energy necessary for even unconstrained enediynes.[95] For example, the presence of the two propyl groups on enediyne **1.120** significantly increases the temperature necessary for cyclisation relative to **1.119**.



BC at 150 °C

1.119

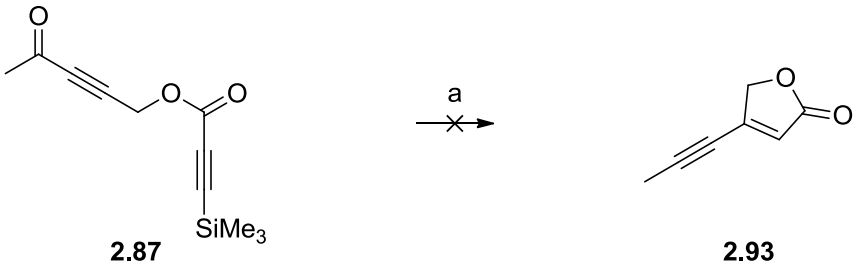


BC >196 °C

1.120

Scheme 2.65: Examples of Enediyens that Undergo the Bergman Cyclisation

As it appeared that the rate of reaction is directly proportional to the temperature as demonstrated in the examples by Nicolaou and co-workers,[95] it should then be possible to cyclise the ketone analogue **2.87** by increasing the temperature. This would increase the statistical chance of the two acetylene moieties to encounter each other in space. To test this hypothesis, different solvents and temperatures were used for the newly discovered transformation; unfortunately no reaction took place (**Table 2.7**).



2.87 **2.93**

Reagents and Conditions: (a) Solvent, time, yield, see **Table 2.7**.

Scheme 2.66: Thermolysis of **2.87**

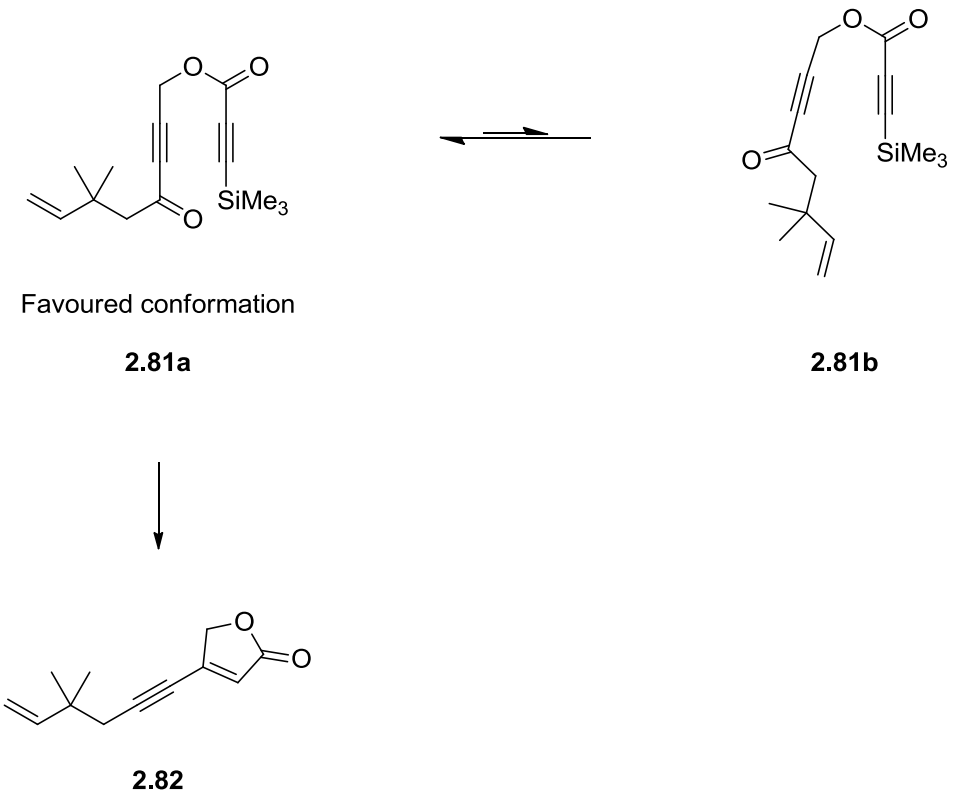
Entry	Solvents	Boiling Temperatures (°C)	Time	Yield (%)
1	DMSO	189	30 min	DM[a]
2	DMF	153	30 min	DM[a]
3	*p*-Xylene	138	30 min	DM[a]

DM[a] = decomposition of material

Table 2.7: Different Conditions Tested for the Thermolysis of **2.87**

It was thought that the reaction temperature in the higher boiling solvents was so hot that thermal decomposition was a likely pathway.

The only obvious difference between this substrate and the successfully cyclised **2.81** is the size of the substituent at the carbonyl centre. It could then be postulated that there is a fundamental necessity for a large substituent to aid the locking of the molecule in a favourable conformation as shown in **Scheme 2.67** below.



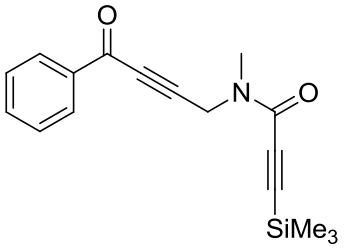
Scheme 2.67: Possible Substituent Effect during Cyclisation of **2.81**

Steric interactions in the precursor **2.87** would be greatly diminished thus limiting the statistical chance of participation of the carbonyl group in the reaction. This may have been aided by the ester linkage which predominantly adopts transoid geometry over the reactive cisoid geometry.

2.8. Investigation through Modification of the Ester Linker

2.8.1. Outline of Investigation

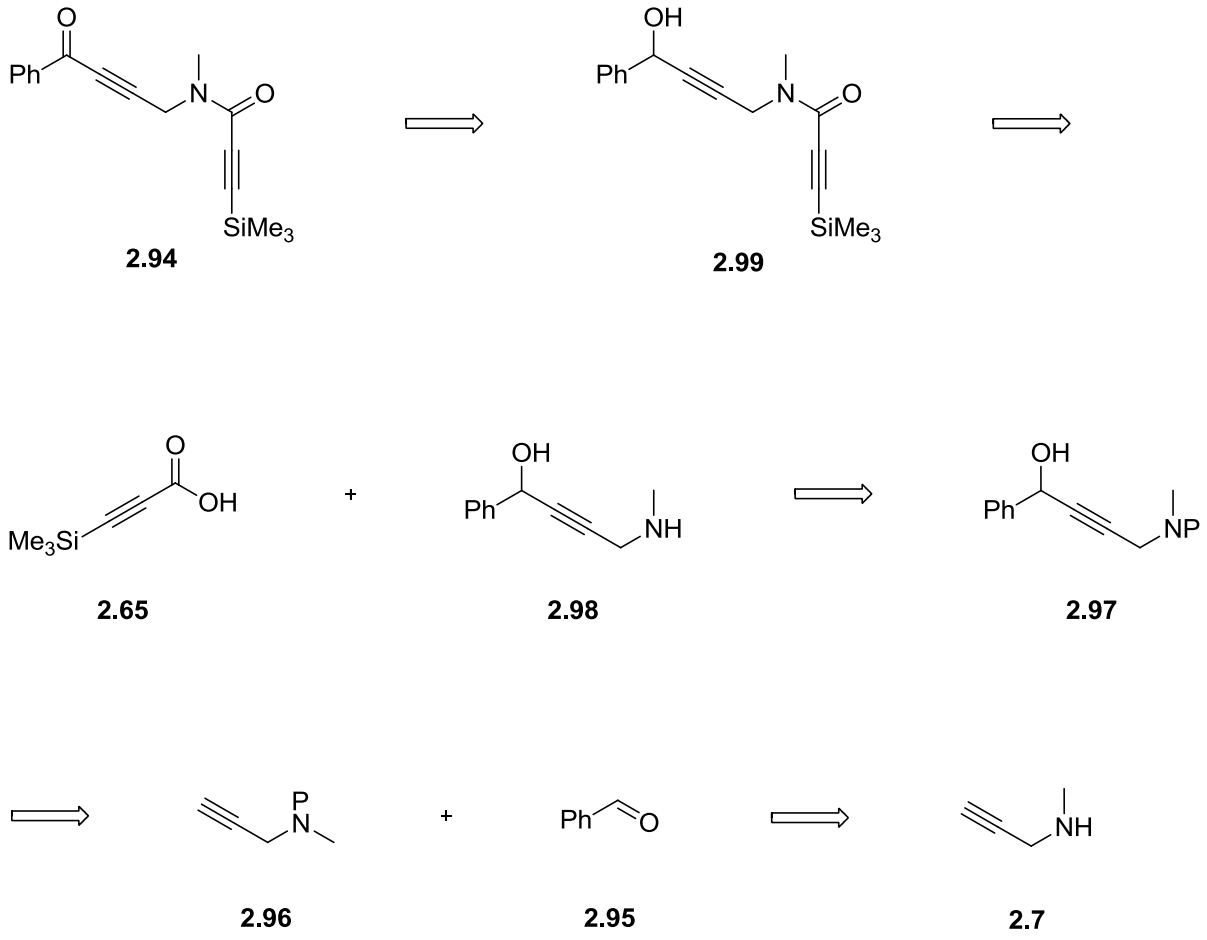
Following the assumption that the cyclisation was disfavoured by the transoid geometry, it was anticipated that exchange of the ester for an amide linker would enhance the cisoid geometry and increase the rate of reaction. Therefore, the chosen course of action was to synthesise a novel cyclisation precursor consisting of a *N*-substituted diyne system with a sterically demanding group attached to carbonyl centre. Due to the immediate availability of benzaldehyde in the laboratory, amide **2.94** was selected as a new synthetic target.



2.94

Figure 2.8: Novel Cyclisation Precursor **2.94**

The retrosynthetic approach for cyclisation precursor **2.94** is depicted in **Scheme 2.68** below.



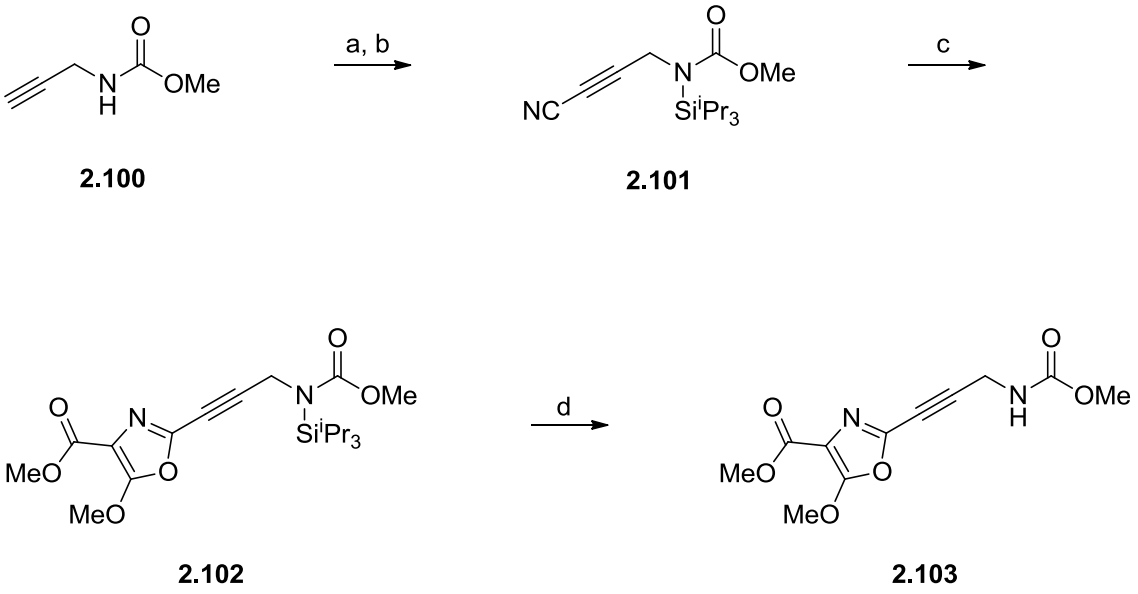
Scheme 2.68: Retrosynthetic Analysis of Cyclisation Precursor **2.94**

Ketone **2.94** can be generated from oxidation of the secondary alcohol **2.99**. A disconnection at the amide moiety in **2.99** leads to the previously synthesised (3-(trimethylsilyl)-2-propynoic acid) **2.65** and secondary amine **2.98**. The latter can be generated from protected amine **2.97** which can be obtained from the alkylation of benzaldehyde **2.95** by the lithium salt of alkyne **2.96**. Furthermore, amine **2.96** can be obtained from commercially available *N*-methylpropargylamine **2.7**.

2.8.2. Synthesis of Cyclisation Precursor 2.94

The difficulties encountered in finding suitable conditions for the Boc-deprotection in **2.3**, led us to identify a different protecting group for the secondary amino-group. Silyl amines are not frequently encountered in organic synthesis due to their sensitivity to moisture, which makes their handling a delicate task.[155] However, they have been successfully employed in

the synthesis of some complex molecules. For example, Wang *et al.*[214] have reported the use of the tri-isopropylsilyl protection in the synthesis of **2.103** (**Scheme 2.69**).



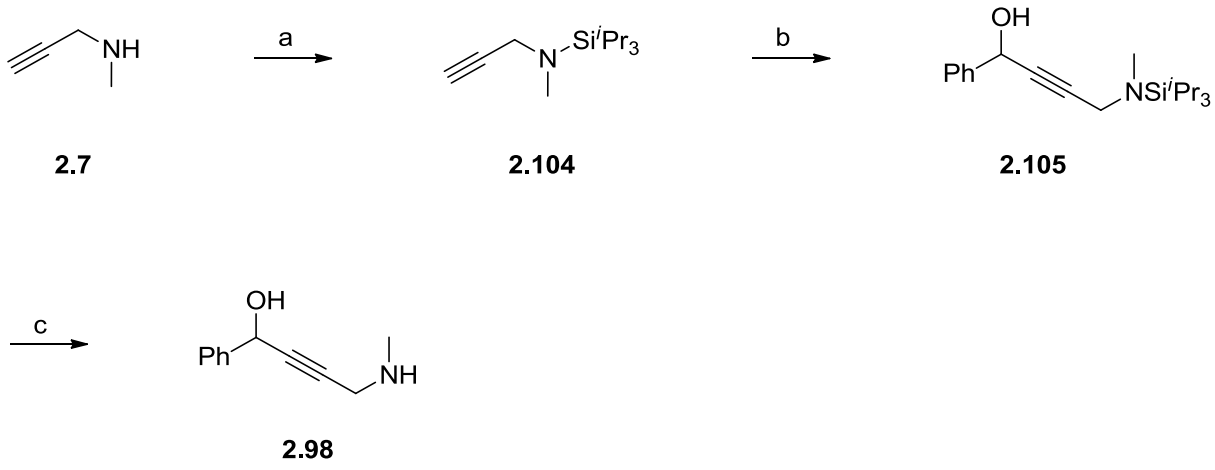
Reagents and Conditions: (a) *n*-BuLi, THF, -78 °C then TIPS-OTf, -78 °C to rt; (b) *n*-BuLi, -78 °C then TsCN, -78 °C to rt 72%; (c) 5 mol% $Rh(OAc)_2$, dimethyl diazomalonate, DCE, reflux; (d) 5M HF in MeCN, rt, 60%.

Scheme 2.69: Work by Wang *et al.*[214]

The silyl amine is stable to *n*-butyllithium and remarkably resilient to a metal carbenoid generated from diazomalonate and rhodium acetate. Silyl removal in this study was performed by action of a solution of hydrofluoric acid in acetonitrile.[214]

All the positive points described above prompted the study of silyl protection for the secondary amino group and due to its availability in the laboratory the tri-isopropylsilyl group was chosen for the investigation.[104]

The adaptation of the silyl protecting group for the synthesis of amine **2.98** is illustrated in **Scheme 2.70** below.



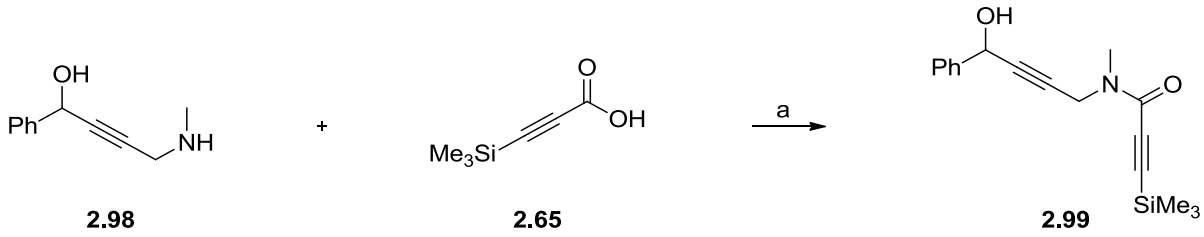
2.7 **2.104** **2.105** **2.98**

Reagents and Conditions: (a) TIPS-OTf, Et_3N, CH_2Cl_2, 0 °C to rt, 16h, 96%; (b) *n*-BuLi, THF, benzaldehyde, - 78 °C to rt, 16h, then sat. aq. NH_4Cl, 96%; (c) 40% aq. HF, MeCN, rt, 30 min., then 10% aq. K_2CO_3, 95%.

Scheme 2.70:Silyl-Protection of *N*-Methylpropargylamine, Alkylation and Silyl-Deprotection

Protection of *N*-methylpropargylamine **2.7** was achieved in quantitative yield with tri-isopropylsilyl trifluoromethanesulfonate in the presence of triethylamine as an acid scavenger (96%). Deprotonation at the terminal acetylene of silyl-protected amine **2.104** and alkylation with a slight excess of benzaldehyde proceeded in 96% yield. After quenching with saturated aqueous ammonium chloride and washing with saturated aqueous sodium bisulfate to remove excess aldehyde *via* its bisulfate adduct,[205] the product **2.105** was found to be adequately pure so further purification was not performed. This also reduces the required time for the synthesis and avoids the potentially problematic column chromatography of the silyl amine. Silyl deprotection of **2.105** was achieved using 40% aqueous hydrofluoric acid in acetonitrile inside a plastic container. A basic work-up furnished desired amine **2.98** as a white, pure solid in 87% yield. This material required no further purification.

Once the amine **2.98** was in hand, formation of amide **2.99** could then be attempted through an amide coupling reaction. The reaction of amine **2.98** with the acyl chloride derived from 3-(trimethylsilyl)-2-propynoic acid **2.65** in the presence of 2,6-lutidine as a base, yielded desired amide **2.99.**

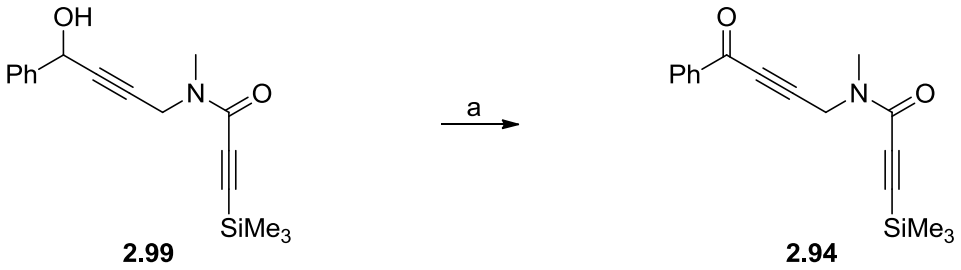


2.98 **2.65** **2.99**

Reagents and Conditions: (a) Oxalyl chloride, $DMF_{(cat.)}$, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 80%.

Scheme 2.71: Synthesis of Amide **2.99**

The next step in the synthetic sequence was the oxidation of the secondary alcohol in newly formed amide **2.99**. Our previous work on the oxidation of acetylenic alcohols prompted our decision to employ chromic acid, generated from chromium(VI) trioxide and concentrated sulfuric acid.



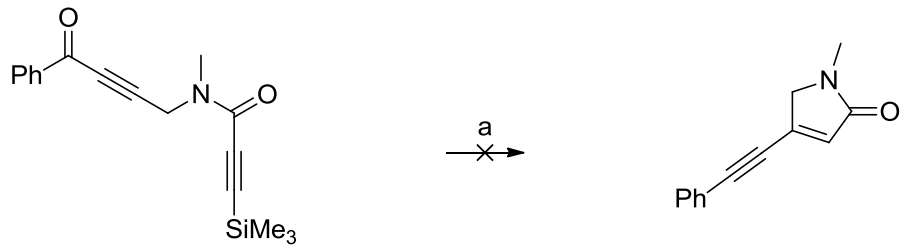
2.99 **2.94**

Reagents and Conditions: (a) 3.0M Jones' reagent, acetone, rt, 96%.

Scheme 2.72: Jones' Oxidation of **2.99**

2.8.3. Thermolysis of 1,6-Diynone 2.94

The next step was to test the thermolysis of **2.94** in refluxing anhydrous, degassed toluene. Identical to previous cyclisations a 0.01M concentration of the starting material was chosen.



2.94 **2.106**

Reagents and Conditions: (a) Toluene, 0.01M, reflux, 24h.

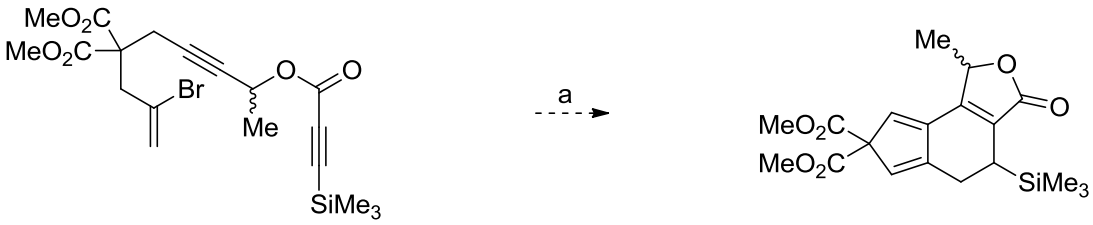
Scheme 2.73: Attempted Cyclisation of **2.94** in Refluxing Toluene

Unfortunately the above thermolysis failed to give any isolable products. A single product was produced which was found to be unstable to moisture, light, prolonged heating in various solvents and mild acidic conditions.

2.9. Investigation through Modification of the Ether Linker

2.9.1. Outline of Investigation

To further investigate the mechanism and scope of the cyclisation, the model system **2.111** was proposed.

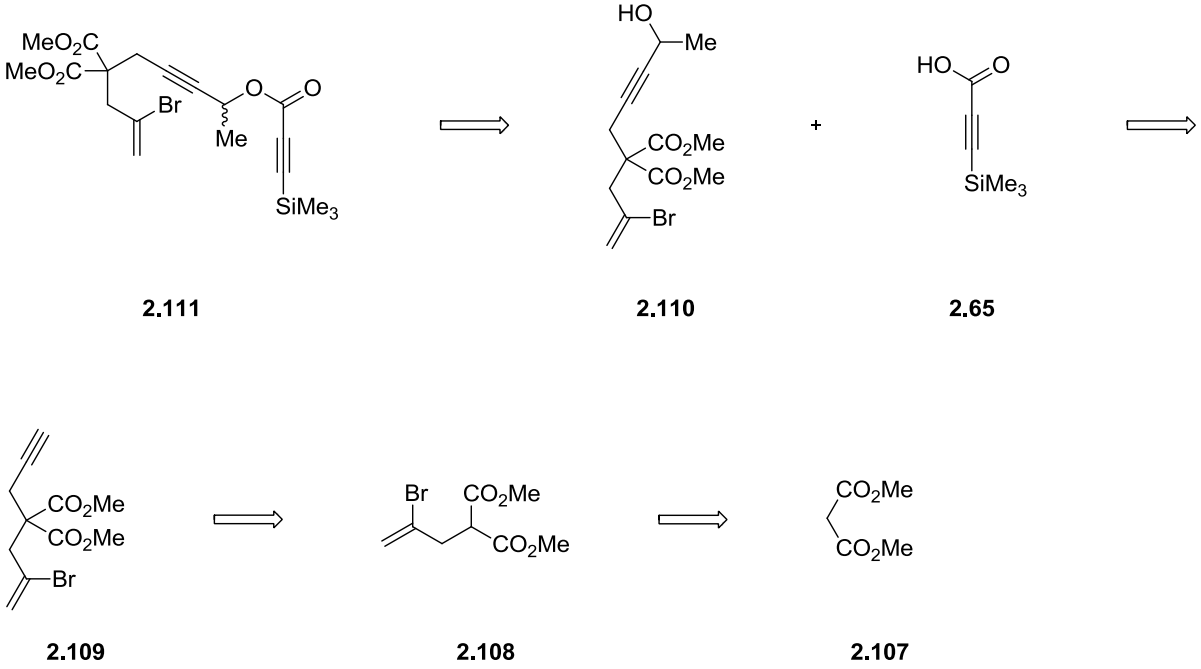


2.111 **2.112**

Figure 2.9: Novel Cyclisation Precursor **2.111**

Conversion of the ether linker to a carbon scaffold was used to assess the versatility of the cyclisation model. Template **2.112** contains indene-2,2-dicarboxylate, lactone functionality and allyl silane, all of which would enable greater diversifications and widely applicable methodology for the construction of polycyclic systems.

The retrosynthetic approach for cyclisation precursor **2.111** is depicted in **Scheme 2.74** below.



2.111 **2.110** **2.65**

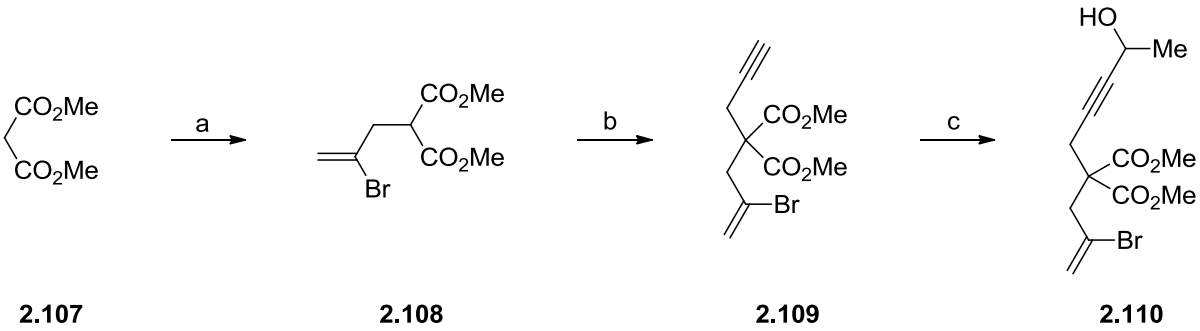
2.109 **2.108** **2.107**

Scheme 2.74: Retrosynthetic Analysis of Cyclisation Precursor **2.111**

A disconnection at the ester moiety leads to the previously synthesised (3-(trimethylsilyl)-2-propynoic acid) **2.65** and alcohol **2.110**. The latter can be easily synthesised by deprotonation of the terminal alkyne in **2.109** and subsequent quenching with acetaldehyde. Alkyne **2.109** can be generated by the reaction of compound **2.108** and the propargyl bromide **2.49**. Furthermore, compound **2.108** can be obtained from commercially available dimethyl malonate **2.107**.

2.9.2. Synthesis of Cyclisation Precursor 2.111

Scheme 2.75 below illustrates the synthesis of desired material **2.111**.

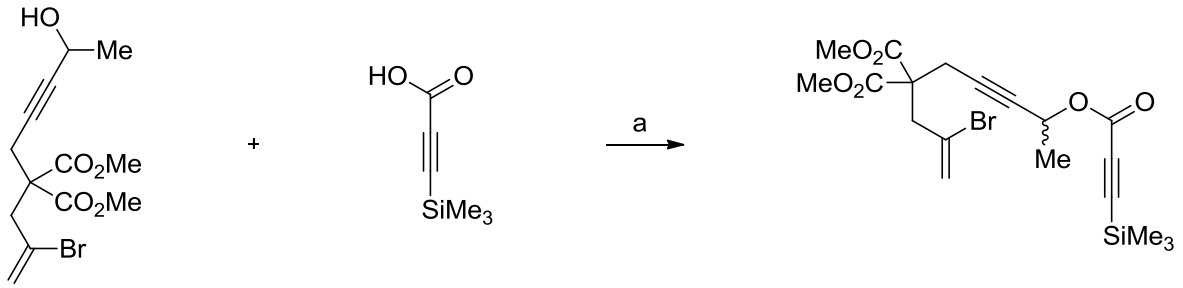


2.107 **2.108** **2.109** **2.110**

Reagents and Conditions: (a) NaH, 2,3-dibromopropene, THF, 0 °C to rt, 16h, 67%; (b) NaH, propargyl bromide, THF, 0 °C to rt, 16h, 96%; (c) *n*-BuLi, THF then acetaldehyde, -78 °C to rt, 16h, 96%.

Scheme 2.75: Synthesis of Alcohol **2.110**

Deprotonation of the dimethyl malonate **2.107** with sodium hydride and treatment with 2,3-dibromopropene afforded the desired compound **2.108** in 67% yield.[215] Propargylation of the compound **2.108** was carried out by using NaH, followed by the addition of propargyl bromide **2.49**. Treatment of the dimethyl 2-(2-bromoallyl)malonate **2.109** with *n*-butyllithium in THF, followed by subsequent addition of acetaldehyde at -78 °C afforded the desired alcohol **2.110**.[139] The reaction of alcohol **2.110** with the acyl chloride derived from 3-(trimethylsilyl)-2-propynoic acid **2.65** in the presence of 2,6-lutidine, as a base yielded desired cyclisation precursor **2.111**.



2.110 **2.65** **2.111**

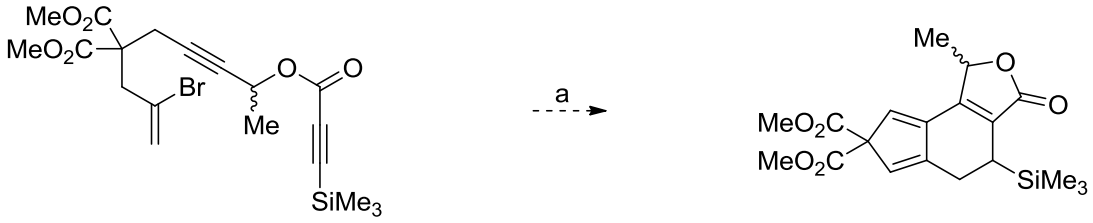
Reagent and Conditions: (a) Oxalyl chloride, $DMF_{(cat.)}$, 2,6-lutidine, CH_2Cl_2, 16h, 69%.

Scheme 2.76: Synthesis of Cyclisation Precursor **2.111**

Advanced intermediate **2.111** was synthesised, however the investigations could not be completed due to time constraints.

Chapter 3.
Conclusion & Future Work

The development of a route for the synthesis of cyclisation precursor **2.111** has been developed and the synthesis of cyclisation precursor **2.111** has successfully achieved. Once cyclisation precursors **2.111** in hand, the standard cyclisation conditions should provide the tricycles **2.112**.

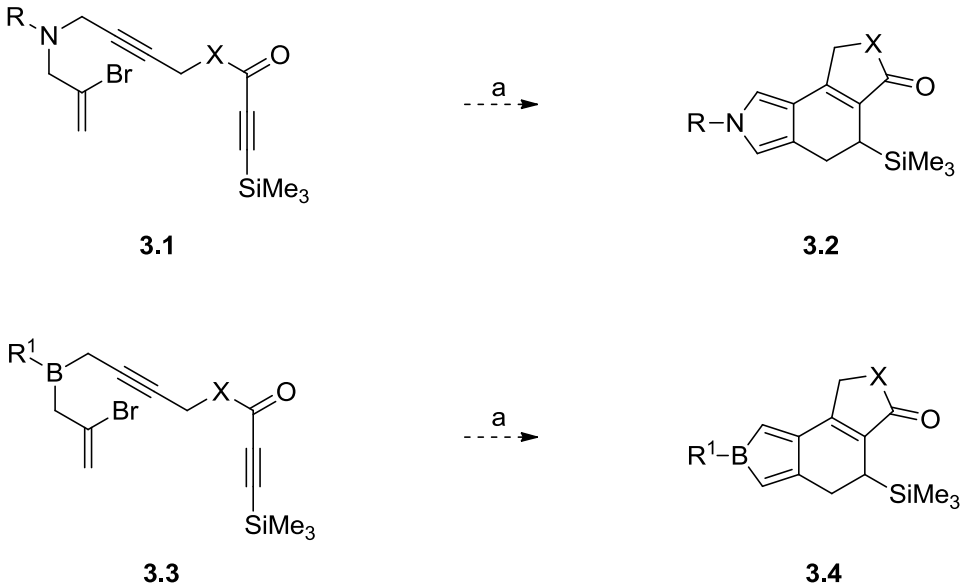


2.111 **2.112**

Reagents and Conditions: (a) Toluene, 0.01M, 1,2-epoxyhexene, reflux.

Scheme 3.1: Thermal Cyclisation of Precursors **2.111**

The overall findings from this DPhil project will enable the rapid construction of complex ring systems as templates for drug design. This evidence gives support to the theory that a range of structures, richly substituted with functional groups could be synthesised using the thermal cyclisation reaction developed within the Parsons' research group.



3.1 **3.2**

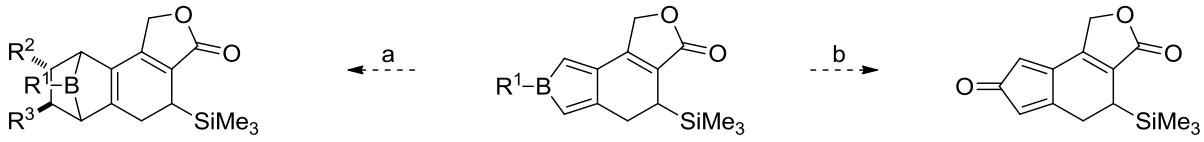
3.3 **3.4**

X : O, NMe R: alkyl, aryl R^1 : thexyl

Reagents and Conditions: (a) Toluene, 0.01M, 1,2-epoxyhexene, reflux.

Scheme 3.2: Construction of Complex Ring Systems

Template **3.2** contains pyrrole and lactone/lactam functionality and allyl silane, all of which can be used to create structural diversity. Boracycles **3.4** can be prepared and their chemistry investigated. The novel chemistry of these compounds will be very exciting as bridge boranes **3.5** can be readily made as well as cyclopentadieneones **3.6**.



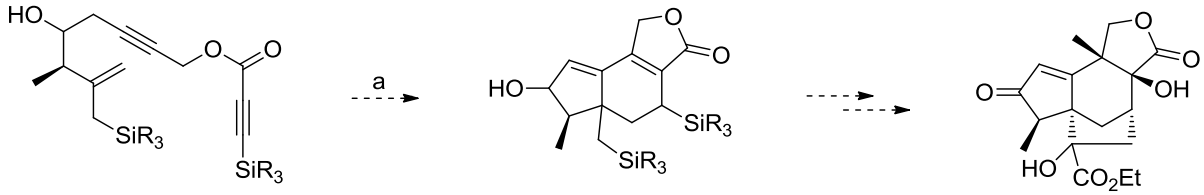
3.5 **3.4** **3.6**

R^1 = thexyl R^2, R^3 = alkyl, aryl

Reagents and Conditions: (a) Diels-Alder; (b) KCN (or CO), H_2O_2.

Scheme 3.3: The Novel Chemistry of Boracycles

Seco-prezizaane-type sesquiterpene Jiadifenin[216] **3.9** is a biologically and structurally interesting molecule that provides the organic chemist with a rewarding synthetic challenge. For example, the tricyclic core of Jiadifenin can be synthesised using the thermal cyclisation reaction discovered within the Parsons' research group.



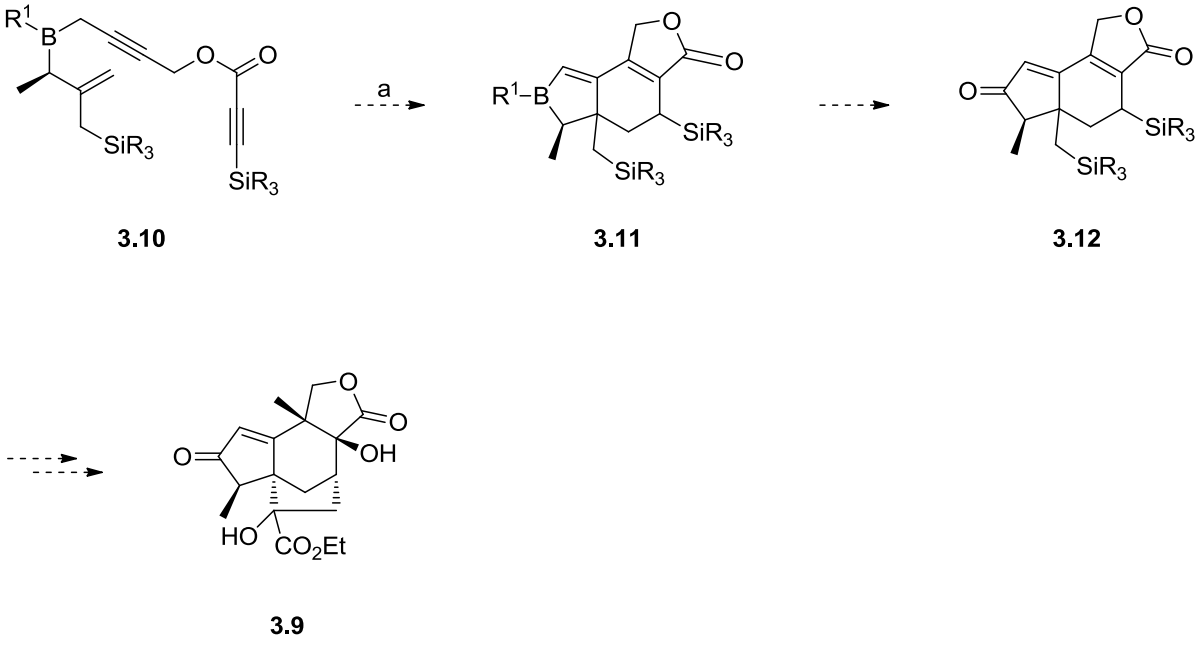
3.7 **3.8** **3.9**

R = alkyl, aryl

Reagents and Conditions: (a) Toluene, 0.01M, reflux.

Scheme 3.4: Proposed Route to Synthesise Tricyclic Core of Jiadifenin

Alternatively the tricyclic core of Jiadifenin can be synthesised using cyclisation precursor **3.10**.



3.10 **3.11** **3.12**

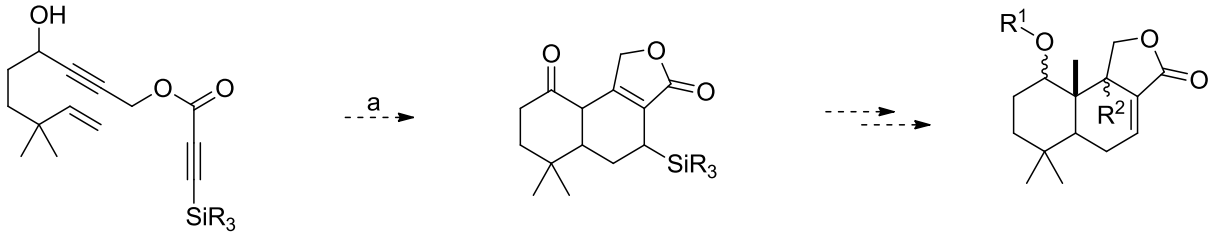
3.9

R^1 = thexyl R = alkyl, aryl

Reagents and Conditions: (a) Toluene, 0.01M, reflux.

Scheme 3.5: Proposed Route to Synthesise Tricyclic Core of Jiadifenin

The biodiversity associated with the drimane-type sesquiterpeniods makes these compounds attractive targets. In addition, the analogues of these structures shown herein allows for diversity in an array of new structures and the synthesis of natural products. The tricyclic core of drimane-type sesquiterpeniods can also be synthesised using the thermal cyclisation reaction developed within the Parsons' research group.

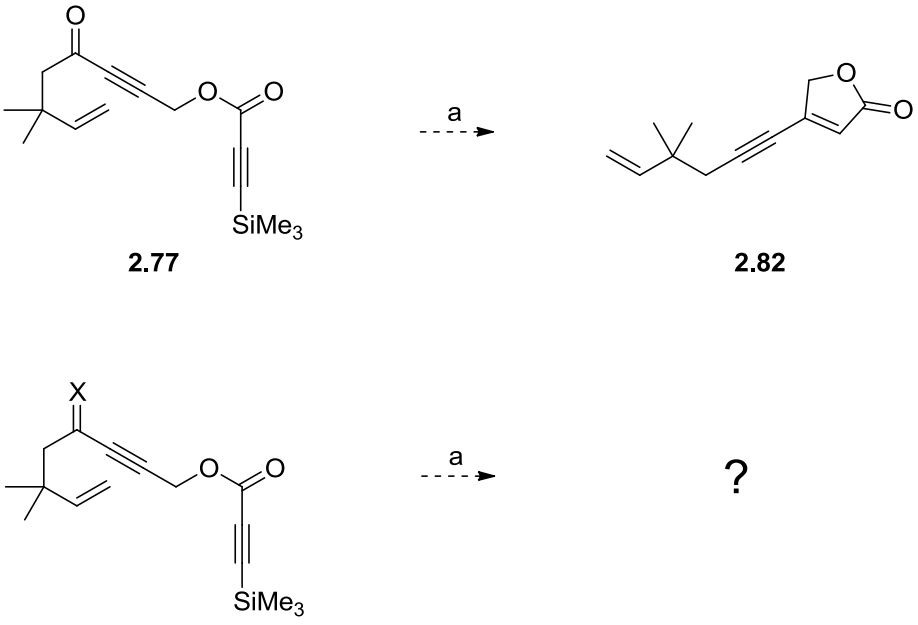


3.13 **3.14** **3.15**

Reagents and Conditions: (a) Toluene, 0.01M, reflux.

Scheme 3.6: Proposed Route to Synthesise Tricyclic Core of Drimane-type Sesquiterpeniods

Furthermore, the 1,6-diynone analogue **2.81** cyclised to give alkyne **2.82**. In order to further investigate this transformation the esters **3.16a-b** can be selected as new synthetic targets.



Reagents and Conditions: (a) Toluene, 0.01M, reflux.

Scheme 2.7: Thermolysis of Cyclisation Precursors **3.16a-b**

Chapter 4. Experimental Section

4.1.General Procedure

Reactions were carried out under a nitrogen atmosphere in oven-dried glassware at room temperature (rt) unless otherwise stated. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Flash column chromatography was carried out on Merck Kieselgel (230-400 mesh). All reactions were followed by thin-layer chromatography (TLC) where possible; using Merck aluminium backed sheets coated with Merck Kieselgel 60 F254 (230-400 mesh) fluorescent treated silica. These were visualised under UV light (λmax= 254 or 365 nm) and developed using potassium permanganate or vanillin stains.

Reaction solvents were purified and dried according to literature methods; tetrahydrofuran and diethyl ether were distilled from sodium with benzophenone as an indicator. CH_2Cl_2, toluene, methanol and acetonitrile were distilled from CaH_2 under a positive pressure of dry nitrogen. Et_3N, 2,6-lutidine and pyridine were also distilled from CaH_2 and stored over KOH under nitrogen. Petroleum ether refers to the fraction boiling at 40-60 °C. Bulk solutions were evaporated under reduced pressure using a rotary evaporator. Other solvents and reagents were used as supplied. Brine refers to a saturated aqueous solution of NaCl. Salicylaldehyde phenylhydrazone was used as an indicator for the titration of organometallic species, including Grignard reagents.

^{1}H NMR spectra were recorded on a Varian 500 MHz machine (operating at ambient probe temperature using an internal deuterium lock). Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: δ/ppm (multiplicity, coupling constant J/Hz (where appropriate), number of protons). Multiplicity is abbreviated as follows: s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, app br d = apparent broad doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplet, q = quartet, dq = doublet of quartet, quint = quintet, m = multiplet, app s = apparent singlet, app d = apparent doublet, app t = apparent triplet, app q = apparent quartet. ^{13}C NMR spectra were recorded at 126 MHz. The ^{13}C NMR spectra are reported in δ/ppm. Two-dimensional (COSY, HSQC, H2BC, HMBC) NMR spectroscopy were used to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra.

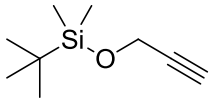
ESI Mass spectra were recorded on a Bruker Daltonics Apex III spectrometer with methanol or diethyl ether as solvents. EI mass spectra were recorded on a Fisons VG Autospec spectrometer by the internal service at the Department of Chemistry, University of Sussex.

IR spectra were recorded neat on a Perkin Elmer Spectrum One FT-IR spectrometer with a diamond ATR module and only selected maximum absorbances (νmax) of the most intense peaks are reported (cm^{-1}).

Melting points were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celsius (°C).

4.2. Compounds

tert-Butyldimethyl(prop-2-yn-1-yloxy)silane: (2.16)



$C_9H_{18}OSi$

To a stirred solution of 2-propynol **2.12** (10.0 g, 178 mmol) in dry CH_2Cl_2 (200 mL) at 0 ºC was added *tert*-butyldimethylsilyl chloride (32.3 g, 214 mmol) and imidazole (30.4 g, 446 mmol). After 1 hour, the reaction mixture was quenched with water. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a colourless liquid. Distillation under reduced pressure afforded 29.74 g (98%) of clear colourless liquid.
Spectroscopic data are in agreement with the literature values.[167]

b.p.: 52 ^{o}C (14 Torr)

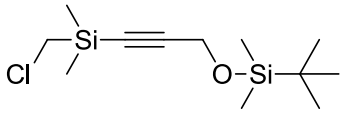
IR (neat) *v* (cm^{-1}) 3312, 2956, 2887, 2859, 2121, 1256, 1098, 838, 779.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (d, *J* = 2.4 Hz, 2H), 2.38 (t, *J* = 2.4 Hz, 1H), 0.92 (s, 9H), 0.13 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 82.4 (C), 72.7 (CH), 51.4 (CH_2), 25.6 (CH_3), 18.1 (C), -5.2 (CH_3).

HRMS (ESI+) calculated for $C_9H_{18}OSi$ $[M]^+$: 170.1127, found: 170.1131.

tert-Butyl((3-((chloromethyl)dimethylsilyl)prop-2-yn-1-yl)oxy)dimethylsilane: (2.17)



$C_{12}H_{25}ClOSi_2$

To a stirred solution of alkyne **2.16** (24.0 g, 141 mmol) in dry THF (250 mL) at -78 ºC was added *n*-BuLi (2.3 M solution in hexanes, 64.4 mL, 148 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of chloro(chloromethyl) dimethylsilane (21.18 g, 19.50 mL, 148 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched at 0 °C with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellowish liquid. The crude product **2.17** was purified by flash chromatography on a silica gel column eluting with 15% diethyl ether in hexanes to give the title compound **2.17** (33 g, 85%) as a pale yellow oil.

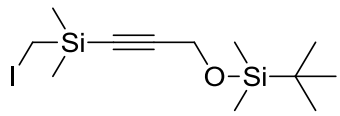
IR (neat) *v* (cm^{-1}) 2930, 2858, 2177, 1470, 1362, 1252, 1092, 816, 777.

^1H NMR (500 MHz, $CDCl_3$) δ 4.30 (s, 2H), 2.83 (s, 2H), 0.90 (s, 9H), 0.29 (s, 6H), 0.13 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 106.5 (C), 85.9 (C), 52.1 (CH_2), 29.7 (CH_2), 25.7 (CH_3), 18.1 (C), -3.4 (CH_3), -5.1 (CH_3).

HRMS (ESI+) calculated for $C_{12}H_{25}ClOSi_2Na$ $[M+Na]^+$: 299.1025, found: 299.1024.

tert-Butyl((3-((iodomethyl)dimethylsilyl)prop-2-yn-1-yl)oxy)dimethylsilane: (2.19)



$C_{12}H_{25}IOSi_2$

To a stirred solution of sodium iodide (21.71 g, 144 mmol) in dry acetone (70 mL) was slowly added a solution of alkyl chloride **2.17** (20.0 g, 72 mmol) in dry acetone (210 mL). The reaction mixture was left to stir at rt for 16 hours. Subsequently, the precipitate was filtered off, washed once with acetone and the solvent was evaporated under reduced pressure to give a yellow oil. The crude product **2.19** was purified by flash chromatography on a silica gel column eluting with 5% diethyl ether in hexanes to give the title compound **2.19** (24.13 g, 91%) as a pale yellow oil.

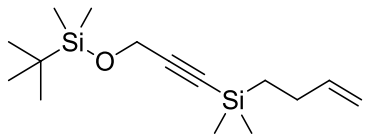
IR (neat) v (cm^{-1}) 2955, 2929, 2857, 2177, 1468, 1363, 1252, 1092, 1001, 813, 776, 715, 674.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (s, 2H), 2.07 (s, 2H), 0.91 (s, 9H), 0.30 (s, 6H), 0.13 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 106.2 (C), 86.4 (C), 52.2 (CH_2), 25.8 (CH_3), 18.2 (C), -1.7 (CH_3), -5.0 (CH_3), -14.5 (CH_2).

HRMS (ESI+) calculated for $C_{12}H_{25}IOSi_2Na$ $[M+Na]^+$: 391.0381, found: 391.0378.

But-3-en-1-yl(3-((*tert*-butyldimethylsilyl)oxy)prop-1-yn-1-yl)dimethylsilane: (2.18)



$C_{15}H_{30}OSi_2$

Preparation of dilithium tetrachlorocuprate(II) solution (Li_2CuCl_4):
To a stirred solution of LiCl (2.12 g, 50 mmol) in dry THF (250 mL) at 0 °C was added $CuCl_2$ (3.36 g, 25 mmol). The approximate molarity of the resultant solution was 0.1M.

Allylmagnesium chloride (2.0 M solution in THF, 40.72 mL, 81.44 mmol) was added to a stirred solution of alkyl iodide 2.19 (15.0 g, 40.72 mmol) in dry THF (75 mL) at 0 °C followed by the addition of a solution of Li_2CuCl_4 (0.1M solution in THF, 203.6 mL, 20.36 mmol). The reaction was allowed to warm to rt and left to stir for 16 hours. Subsequently, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give an dark yellow liquid. The crude product **2.18** was purified by flash chromatography on a silica gel column eluting with 5% diethyl ether in hexanes to give the title compound **2.18** (8.56 g, 77%) as a yellow oil.

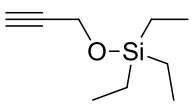
IR (neat) *v* (cm^{-1}) 2956, 2926, 2905, 2857, 2177, 1640, 1472, 1467, 1362, 1252, 1093, 1000, 833, 777, 722, 648, 663, 621.

^1H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddt, *J* = 16.5, 10.1, 6.2 Hz, 1H), 5.01 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.90 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.25 (s, 2H), 2.20 – 2.12 (m, 2H), 0.92 (s, 9H), 0.75 – 0.70 (m, 2H), 0.17 (s, 3H), 0.16 (s, 3H), 0.13 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0 (CH), 112.9 (CH_2), 105.2 (C), 88.5 (C), 52.2 (CH_2), 27.8 (CH_2), 25.7 (CH_3), 18.2 (C), 15.1 (CH_2), -0.2 (CH_3), -1.7 (CH_3), -5.0 (CH_3).

HRMS (ESI+) calculated for $C_{15}H_{30}OSi_2Na$ $[M+Na]^+$: 305.1727, found: 305.1723.

Triethyl(prop-2-yn-1-yloxy)silane: (2.22)



$C_9H_{18}OSi$

To a stirred solution of 2-propynol **2.12** (10.0 g, 178 mmol) in DMF (200 mL) at 0 ºC was added chlorotriethylsilane (32.25 g, 214 mmol) and imidazole (30.4 g, 446 mmol). After 1 hour, the reaction mixture was quenched with 1% aqueous Na_2CO_3 solution. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a pale yellow liquid. Distillation under reduced pressure afforded 26.07 g (86%) of clear colourless liquid.
Spectroscopic data are in agreement with the literature values.[187]

b.p.: 74 – 75 °C (15 Torr).

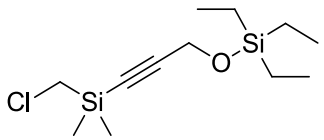
IR (neat) *v* (cm^{-1}) 3313, 2955, 2911, 2875, 2122, 1459, 1413, 1371, 1238, 1068, 1003, 971, 726, 664.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (d, *J* = 2.4 Hz, 2H), 2.39 (t, *J* = 2.4 Hz, 1H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.66 (q, *J* = 7.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 82.3 (C), 72.7 (CH), 51.1 (CH_2), 6.6 (CH_3), 4.4 (CH_2).

HRMS (ESI+) calculated for $C_9H_{18}OSiNa$ $[M+Na]^+$: 193.1019, found: 193.1023.

(Chloromethyl)dimethyl(3-((triethylsilyl)oxy)prop-1-yn-1-yl)silane: (2.23)



$C_{12}H_{25}ClOSi_2$

To a stirred solution of alkyne **2.22** (24.0 g, 141 mmol) in dry THF (250 mL) at -78 ºC was added *n*-BuLi (2.3 M solution in hexanes, 64.4 mL, 148 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of chloro(chloromethyl) dimethylsilane (21.18 g, 19.50 mL, 148 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched at 0 °C with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellowish liquid. The crude product **2.23** was purified by flash chromatography on a silica gel column eluting with 15% diethyl ether in hexanes to give the title compound **2.23** (33 g, 85%) as a pale yellow oil.

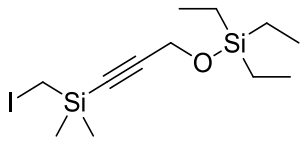
IR (neat) ν (cm^{-1}) 2956, 2929, 2901, 2857, 2181, 1472, 1362, 1252, 1095, 1003, 835, 722, 648.

^1H NMR (500 MHz, $CDCl_3$) δ 4.31 (s, 2H), 2.84 (s, 2H), 0.98 (t, J = 7.9 Hz, 9H), 0.66 (q, J = 7.9 Hz, 6H), 0.29 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 106.3 (C), 85.8 (C), 51.7 (CH_2), 29.8 (CH_2), 6.6 (CH_3), 4.4 (CH_2), -3.4 (CH_3).

Ion not found

Triethyl((3-((iodomethyl)dimethylsilyl)prop-2-yn-1-yl)oxy)silane: (2.24)



$C_{12}H_{25}IOSi_2$

To a stirred solution of sodium iodide (21.71 g, 144 mmol) in dry acetone (70 mL) was added a solution of alkyl chloride **2.23** (20.0 g, 72 mmol) in dry acetone (210 mL). The reaction mixture was stirred at rt for 16 hours. Subsequently, the precipitate was filtered off, washed once with acetone and the solvent was evaporated under reduced pressure to give a yellow oil. The crude product **2.24** was purified by flash chromatography on a silica gel column eluting with 5% diethyl ether in hexanes to give the title compound **2.24** (23.41 g, 88%) as a yellow oil.

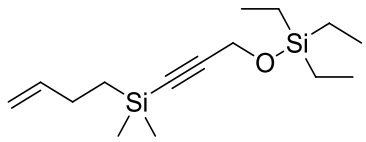
IR (neat) ν (cm^{-1}) 2955, 2911, 2876, 2179, 1458, 1375, 1255, 1060, 836, 800, 726, 690.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (s, 2H), 2.07 (s, 2H), 0.98 (t, J = 7.9 Hz, 9H), 0.66 (q, J = 7.9 Hz, 6H), 0.30 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 106.0 (C), 86.3 (C), 51.8 (CH_2), 6.6 (CH_3), 4.4 (CH_2), -1.7 (CH_3), -14.6 (CH_2).

HRMS (ESI+) calculated for $C_{12}H_{25}IOSi_2Na$ $[M+Na]^+$: 391.0381, found: 391.0371.

But-3-en-1-yldimethyl(3-((triethylsilyl)oxy)prop-1-yn-1-yl)silane: (2.25)



$C_{15}H_{30}OSi_2$

Allylmagnesium chloride (2.0 M solution in THF, 40.72 mL, 81.44 mmol) was added to a stirred solution of alkyl iodide **2.24** (15.0 g, 40.72 mmol) in dry THF (75 mL) at 0 °C followed by addition of a solution of Li_2CuCl_4 (0.1M solution in THF, 203.6 mL, 20.36 mmol). The reaction was allowed to warm to rt and left to stir for 16 hours. Subsequently, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give an orange liquid. The crude product **2.25** was purified by flash chromatography on a silica gel column eluting with 5% diethyl ether in hexanes to give the title compound **2.25** (9.20 g, 80%) as a yellow oil.

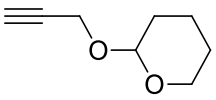
IR (neat) *v* (cm^{-1}) 2956, 2912, 2878, 2177, 1640, 1459, 1413, 1363, 1250, 1090, 1000, 840 814, 776.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 16.6, 10.2, 6.3 Hz, 1H), 5.01 (dd, *J* = 17.0, 1.6 Hz, 1H), 4.90 (dd, *J* = 10.1, 1.1 Hz, 1H), 4.32 (s, 2H), 2.19 – 2.11 (m, 2H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.75 – 0.71 (m, 2H), 0.66 (q, *J* = 7.9 Hz, 6H), 0.17 (s, 3H), 0.16 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1 (CH), 112.9 (CH_2), 105.0 (C), 88.4 (C), 51.8 (CH_2), 27.8 (CH_2), 15.1 (CH_2), 6.6 (CH_3), 4.5 (CH_2), -0.3 (CH_3), -1.9 (CH_3).

HRMS (ESI+) calculated for $C_{15}H_{30}OSi_2Na$ $[M+Na]^+$: 305.1727, found: 305.1723.

2-(Prop-2-yn-1-yloxy)tetrahydro-*2H*-pyran: (2.27)



$C_8H_{12}O_2$

Propargyl alcohol **2.12** (8.41 g, 150 mmol) was added dropwise to a stirring solution of 3,4-dihydro-*2H*-pyran (18.93 g, 225 mmol) and *para*-toluenesulphonic acid monohydrate (7.5 mg) in CH_2Cl_2 (225 mL) at 0 °C. The reaction was allowed to warm to rt and left to stir for 4 hours. Subsequently, the resultant solution was diluted with diethyl ether and washed once with half-saturated brine to remove the catalyst, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a pale yellow oil. The crude product **2.27** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.27** (19.97 g, 95%) as a colourless oil.
Spectroscopic data are in agreement with the literature values.[217]

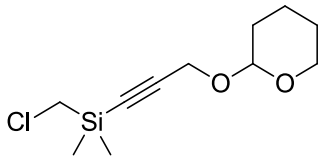
IR (neat) ν (cm^{-1}) 3291, 2942, 2879, 2122, 1442, 1350, 1261, 1202, 1118, 1023, 954, 874, 816.

^1H NMR (500 MHz, $CDCl_3$) δ 4.77 (t, J = 3.1 Hz, 1H), 4.27 (dd, J = 15.7, 2.5 Hz, 1H), 4.22 (dd, J = 15.7, 2.5 Hz, 1H), 3.84 – 3.78 (m, 1H), 3.53 – 3.44 (m, 1H), 2.38 (t, J = 2.4 Hz, 1H), 1.85 – 1.42 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 96.7 (CH), 79.7 (C), 73.9 (CH), 61.8 (CH_2), 53.8 (CH_2), 30.1 (CH_2), 25.2 (CH_2), 18.1 (CH_2).

HRMS (ESI+) calculated for $C_8H_{12}O_2Na$ $[M+Na]^+$: 163.0781, found: 163.0779.

(Chloromethyl)dimethyl(3-((tetrahydro-*2H*-pyran-2-yl)oxy)prop-1-yn-1-yl)silane: (2.28)



$C_{11}H_{19}ClO_2Si$

To a stirred solution of alkyne **2.27** (18.0 g, 128 mmol) in dry THF (200 mL) at -78 ºC was added *n*-BuLi (2.3 M solution in hexanes, 58.69 mL, 135 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of chloro(chloromethyl) dimethylsilane (19.32 g, 17.79 mL, 135 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched at 0 °C with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow liquid. The crude product **2.28** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.28** (29.25 g, 89%) as a yellow oil.

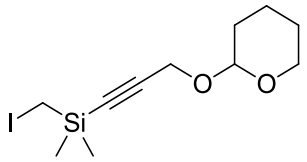
IR (neat) *v* (cm^{-1}) 2942, 2870, 2854, 2179, 1443, 1391, 1343, 1253, 1120, 1060, 1026, 802, 815, 795.

^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (t, *J* = 3.4 Hz, 1H), 4.32 – 4.22 (m, 2H), 3.87 – 3.80 (m, 1H), 3.57 – 3.51 (m, 1H), 2.86 (s, 2H), 1.88 – 1.49 (m, 6H), 0.30 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 103.6 (C), 96.7 (CH), 87.0 (C), 61.8 (CH_2), 54.7 (CH_2), 30.1 (CH_2), 29.0 (CH_2), 25.1 (CH_2), 18.2 (CH_2), -3.8 (CH_3).

HRMS (ESI+) calculated for $C_{11}H_{19}ClO_2SiNa$ $[M+Na]^+$: 269.0729, found: 269.0735.

(Iodomethyl)dimethyl(3-((tetrahydro-*2H*-pyran-2-yl)oxy)prop-1-yn-1-yl)silane: (2.29)



$C_{11}H_{19}IO_2Si$

To a stirred solution of sodium iodide (26.72 g, 178 mmol) in dry acetone (70 mL) was slowly added a solution of alkyl chloride **2.28** (22.0 g, 89 mmol) in dry acetone (210 mL). The reaction mixture was stirred at rt for 16 hours. After which time, the precipitate was filtered off, washed once with acetone and the solvent was evaporated under reduced pressure to give a yellow oil. The crude product **2.29** was purified by flash chromatography on a silica gel column eluting with 10% diethyl ether in hexanes to give the title compound **2.29** (24.69 g, 82%) as a yellow oil.

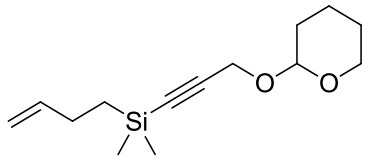
IR (neat) *v* (cm^{-1}) 2941, 2875, 2854, 2183, 1440, 1343, 1252, 1120, 1025, 814, 713, 673, 652,

^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (t, *J* = 3.3 Hz, 1H), 4.31 – 4.20 (m, 2H), 3.86 – 3.78 (m, 1H), 3.55 – 3.48 (m, 1H), 2.07 (s, 2H), 1.88 – 1.47 (m, 6H), 0.30 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 103.3 (C), 96.7 (CH), 87.6 (C), 61.9 (CH_2), 54.6 (CH_2), 30.2 (CH_2), 25.3 (CH_2), 18.9 (CH_2), -1.6 (CH_3), -14.5 (CH_2).

HRMS (ESI+) calculated for $C_{11}H_{19}IO_2SiNa$ $[M+Na]^+$: 361.0100, found: 361.0091.

But-3-en-1-yldimethyl(3-((tetrahydro-*2H*-pyran-2-yl)oxy)prop-1-yn-1-yl)silane: (2.30)



$C_{14}H_{24}O_2Si$

Allylmagnesium chloride (2.0 M solution in THF, 53.21 mL, 106.0 mmol) was added to a stirred solution of alkyl iodide **2.29** (18.0 g, 53.0 mmol) in dry THF (80 mL) at 0 °C followed by the addition of a solution of Li_2CuCl_4 (0.1M solution in THF, 265.0 mL, 26.5 mmol). The reaction was allowed to warm to rt and left to stir for 16 hours. Subsequently, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a pale orange liquid. The crude product **2.30** was purified by flash chromatography on a silica gel column eluting with 10% diethyl ether in hexanes to give the title compound **2.30** (10.16 g, 76%) as a yellow oil.

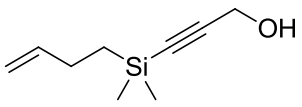
IR (neat) *v* (cm^{-1}) 2945, 2930, 2875, 2853, 2176, 1642, 1442, 1344, 1251, 1120, 1026, 992, 900, 840, 817, 779, 696.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddt, *J* = 16.6, 10.2, 6.3 Hz, 1H), 5.00 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.90 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.81 (app. dd, *J* = 7.2, 3.6 Hz, 1H), 4.30 – 4.19 (m, 2H), 3.86 – 3.80 (m, 1H), 3.55 – 3.49 (m, 1H), 2.16 – 2.10 (m, 2H), 1.87 – 1.49 (m, 6H), 0.75 – 0.70 (m, 2H), 0.17 (s, 3H), 0.16 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) *Anomer A:* δ 140.8 (CH), 112.9 (CH_2), 102.2 (C), 96.6 (CH), 89.7 (C), 61.9 (CH_2), 54.7 (CH_2), 30.2 (CH_2), 27.8 (CH_2), 25.3 (CH_2), 19.0 (CH_2), 15.1 (CH_2), -0.2 (CH_3), -1.7 (CH_3); *Anomer B:* δ 101.5 (C), 96.7 (CH), 90.7 (C), 61.8 (CH_2), 54.7 (CH_2), 30.2 (CH_2), 19.9 (CH_2).

HRMS (ESI+) calculated for $C_{14}H_{24}O_2SiNa$ $[M+Na]^+$: 275.1438, found 275.1435.

3-(But-3-en-1-yldimethylsilyl)prop-2-yn-1-ol: (2.20)



$C_9H_{16}OSi$

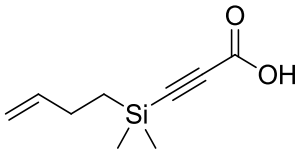
To a stirred solution of tetrahydropyranyl ether **2.30** (3.80 g, 15.07 mmol) in methanol (30 mL) was added pyridinium *para*-toluenesulfonate **(**PPTS; 3 mg). The reaction was stirred at rt for 3 hours and then quenched with saturated aqueous $NaHCO_3$ solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.20** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.20** (0.98 g, 39%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 5.84 (ddt, *J* = 16.5, 10.2, 6.2 Hz, 1H), 4.97 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.86 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.20 (s, 2H), 3.05 (br s, 1H), 2.12 – 2.06 (m, 2H), 0.71 – 0.65 (m, 2H), 0.12 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9 (CH), 113.0 (CH_2), 104.7 (C), 89.1 (C), 51.6 (CH_2), 27.7 (CH_2), 15.0 (CH_2), -0.2 (CH_3), -1.8 (CH_3).

HRMS (ESI+) calculated for $C_9H_{16}OSiNa$ $[M+Na]^+$: 191.0981, found 191.0992.

3-(But-3-en-1-yldimethylsilyl)propiolic acid: (2.4)



$C_9H_{14}O_2Si$

Preparation of Jones' reagent:

To a stirred solution of chromium(VI) trioxide (67 g, 670 mmol) in water (125 mL) at 0 °C was carefully added concentrated H_2SO_4 (110.2 g, 58 mL, 1.124 mol). Residual salts at the bottom of the flask were then dissolved using the minimum quantity of water necessary. The approximate molarity of the resultant solution was 3.0M.

To a stirred solution of tetrahydropyranyl ether **2.30** (6.0 g, 35.65 mmol) in acetone (75 mL) at 0 °C was slowly added Jones' reagent (3.0M solution, 35.65 mL, 106.95 mmol). The resultant mixture was stirred at 0 °C for 1 hour, it was then allowed to warm to rt and stirred for a further 3 hours. Subsequently, the reaction mixture was quenched with water, the phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a pale brown liquid. The crude product 16 was used directly in the next step without future purifications (6.49, 96%).

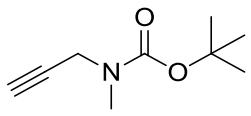
IR (neat) *v* (cm^{-1}) 2964, 2930, 2176, 1690, 1406, 1252, 1054, 994, 908, 843, 822, 784,760, 731.

^1H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 10.48 (br s, 1H), 5.87 (ddt, *J* = 16.5, 10.1, 6.3 Hz, 1H), 4.99 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.89 (dd, *J* = 10.1, 1.4 Hz, 1H), 2.19 – 2.12 (m, 2H), 0.83 – 0.78 (m, 2H), 0.24 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.9 (C), 140.2 (CH), 113.6 (CH_2), 96.0 (C), 94.5 (C), 27.5 (CH_2), 14.2 (CH_2), -2.5 (CH_3).

Ion not found

tert-Butyl methyl(prop-2-yn-1-yl)carbamate: (2.6)



$C_9H_{15}NO_2$

To a stirred solution of *N*-methylpropargylamine **2.7** (4.00 g, 57.9 mmol) and pyridine (5.49 g, 5.59 mL 69.5 mmol) in dry diethyl ether (100 mL) at 0 °C was added di-*tert*-butyl dicarbonate (15.2 g, 69.5 mmol). The resultant solution was allowed to warm to rt and left to stir for 16 hours. Subsequently, the reaction mixture was quenched with water, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.6** was purified by flash chromatography on a silica gel column eluting with 10% diethyl ether in petroleum ether to give the title compound **2.6** (9.4 g, 96%) as a clear colourless oil.
Spectroscopic data are in agreement with the literature values.[139]

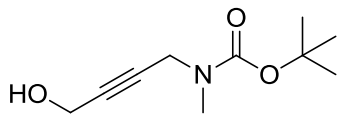
IR (neat) ν (cm^{-1}) 3308, 2978, 2933, 1699, 1482, 1454, 1421, 1392, 1368, 1249, 1152, 1050.

^1H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 4.00 (br s, 2H), 2.87 (s, 3H), 2.17 (t, J = 2.5 Hz, 1H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0 (C), 80.0 (C), 79.0 (C), 71.4 (CH), 37.8 (CH_2), 33.2 (CH_3), 28.2 (CH_3).

HRMS (ESI+) calculated for $C_9H_{15}NO_2Na$ $[M+Na]^+$: 192.0900, found: 192.0995.

tert-Butyl (4-hydroxybut-2-yn-1-yl)(methyl)carbamate: (2.5)



$C_{10}H_{17}NO_3$

To a stirred solution of alkyne **2.6** (4.0 g, 23.6 mmol) in dry THF (80 mL) at -78 ºC was added *n*-BuLi (2.3 M solution in hexanes, 11.3 mL, 26.0 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of powdered paraformaldehyde (1.42 g, 47.3 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched at 0 °C with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellowish liquid. The crude product **2.5** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.5** (4.70 g, 78%) as a pale yellow oil.
Spectroscopic data are in agreement with the literature values.[139]

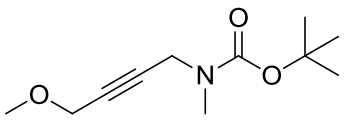
IR (neat) *v* (cm^{-1}) 3411, 2975, 2932, 2870, 1681, 1480, 1451, 1398, 1366, 1349, 1248, 1230, 1145, 1128, 1048, 1023, 869, 771, 666.

^1H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 4.22 (s, 2H), 4.02 (s, 2H), 2.94 (br s, 1H), 2.85 (s, 3H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7 (C), 82.0 (C), 80.5 (C), 80.1 (C), 50.7 (CH_2), 38.0 (CH_2), 33.4 (CH_3), 28.3(CH_3).

HRMS (ESI+) calculated for $C_{10}H_{17}NO_3Na$ $[M+Na]^+$: 222.1101, found: 222.1107.

tert-Butyl (4-methoxybut-2-yn-1-yl)(methyl)carbamate: (2.3)



$C_{11}H_{19}NO_3$

To dimethyl sulfoxide (DMSO; 40 mL) was added powder potassium hydroxide (4.50 g, 80.08 mmol). After stirring the suspension for 5 minutes the substrate **2.5** (4.0 g, 20.07 mmol) was added, followed by immediate addition of methyl iodide (5.69 g, 2.49 ml, 40.14 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched with water. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.3** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.3** (3.85 g, 90%) as a yellow oil.

IR (neat) *v* (cm^{-1}) 2977, 2932, 2898, 2252, 1693, 1452, 1367, 1249, 1142, 1123.

^{1}H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 4.06 (s, 2H), 4.03 (br s, 2H), 3.33 (s, 3H), 2.86 (s, 3H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9 (C), 81.8 (C), 79.9 (C), 79.1 (C), 59.8 (CH_2), 57.1 (CH_3), 38.0 (CH_2), 33.3 (CH_3), 28.1 (CH_3).

HRMS (ESI+) calculated for $C_{11}H_{19}NO_3Na$ $[M+Na]^+$: 236.1262, found: 236.1257.

4-Methoxy-*N*-methylbut-2-yn-1-amine hydrochloride: (2.15)

$C_6H_{12}ClNO$

To a stirred solution of *N*-Boc amine **2.3** (3.5 g, 16.42 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added a 4.0 M solution of HCl in dioxane (98.52 mL, 394.08 mmol). The reaction mixture was allowed to warm to rt and left to stir for 4 hours, during which time the formation of brown precipitates were observed. The solvent was removed *in vacuo* to afford a brown solid. This solid was triturated with diethyl ether to afford a dark brown amorphous solid which was collected by filtration and washed well with diethyl ether, after drying under high vacuum the title product obtained was a brown amorphous solid. The crude product **2.15** was used directly in the next step without future purifications (1.74, 71%).

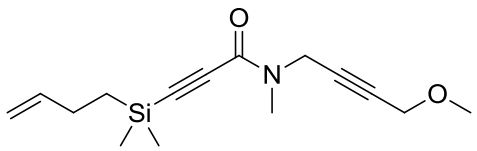
IR (neat) ν (cm^{-1}) 3377, 2940, 1633, 1465, 1360, 1123, 1188, 1087.

^1H NMR (500 MHz, DMSO-d_6) δ 4.14 (t, J = 1.9 Hz, 2H), 3.90 (s, 2H), 3.24 (s, 3H), 2.55 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 84.8 (C), 77.5 (C), 59.3 (CH_2), 57.5 (CH_3), 37.4 (CH_2), 31.9 (CH_3).

HRMS (ESI+) calculated for $C_6H_{13}ClNO$ $[M+H]^+$: 150.0700, found: 150.0680.

3-(But-3-en-1-yldimethylsilyl)-*N*-(4-methoxybut-2-yn-1-yl)-*N*-methylpropiolamide: (2.1)



$C_{15}H_{23}NO_2Si$

To a stirred solution of carboxylic acid **2.4** (1.0 g, 5.48 mmol) and 4 drops of DMF in dry CH_2Cl_2 (10 mL) at 0 °C was added oxalyl chloride (0.73 g, 0.49 mL, 5.75 mmol). The solution was allowed to warm to rt and left to stir for 2 hours. This was added to a solution of propargylic amine **2.15** (1.23 g, 8.22 mmol) and 2,6-lutidine (1.77 g, 1.91 mL, 16.44 mmol) in dry CH_2Cl_2 (20 mL) which had been stirring for 30 minutes. The resultant cloudy solution was allowed to warm to rt and left to stir for 16 hours. The reaction mixture was then quenched with water, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.1** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.1** (0.98 g, 71%) as a yellow oil.

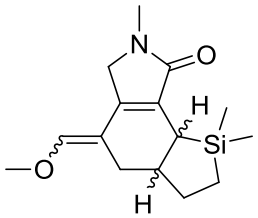
IR (neat) *v* (cm^{-1}) 2926, 2850, 1685, 1634, 1443, 1251, 1234, 1120, 1094, 843.

^{1}H NMR (500 MHz, $CDCl_3$, resolved signals of rotamers) *Rotamer A*: δ 5.86 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 1H), 5.02 – 4.98 (m, 1H), 4.93 – 4.87 (m, 1H), 4.26 (s, 1H), 4.07 (s, 1H), 3.34 (s, 1.5H), 3.24 (s, 1.5H), 2.18 – 2.12 (m, 2H), 0.78 – 0.73 (m, 2H), 0.23 (s, 3H), 0.21 (s, 3H); *Rotamer B*: δ 4.41 (s, 1H). 4.09 (s, 1H), 3.35 (s, 1.5H), 2.99 (s, 1.5H).

^{13}C NMR (126 MHz, $CDCl_3$, resolved signals of rotamers) *Rotamer A*: δ 153.4 (C), 140.4 (CH), 113.4 (CH_2), 97.0 (C), 96.2 (C), 80.1 (C), 80.0 (C), 59.8 (CH_2), 57.6 (CH_3), 35.4 (CH_3), 35.3 (CH_2), 27.6 (CH_2), 14.5 (CH_2), -0.7 (CH_3), -2.3 (CH_3); *Rotamer B*: δ 97.0 (C), 96.0 (C), 80.7 (C), 80.0 (C), 59.7 (CH_2), 40.8 (CH_2), 31.5 (CH_3).

HRMS (ESI+) calculated for $C_{15}H_{23}NO_2SiNa$ $[M+Na]^+$: 300.1429, found: 300.1428.

5-(Methoxymethylene)-1,1,7-trimethyl-1,3,3a,4,5,6,7,8b-octahydrosilolo[2,3-e]isoindol-8(*2H*)-one: (2.2)



$C_{15}H_{23}NO_2Si$

A solution of 3-(but-3-en-1-yldimethylsilyl)-*N*-(4-methoxybut-2-yn-1-yl)-*N*-methylpropiol amide **2.1** (0.5 g, 1.80 mmol) in de-gassed toluene (180 mL) was heated at reflux for 16 hours. After cooling to rt the solvent was removed *in vacuo* and the crude product **2.2** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.2** (0.19 g, 38%) as a yellow oil.

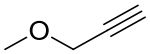
IR (neat) *v* (cm^{-1}) 2960, 2923, 2854, 1678, 1456, 1400, 1379, 1252, 1177, 11261, 1048, 841, 798.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (s, 1H), 4.19 – 4.06 (m, 2H), 3.65 (s, 3H), 3.04 (s, 3H), 2.35 – 2.27 (m, 1H), 2.07 – 0.82 (m, 5H), 0.75 – 0.69 (m, 2H), 0.33 (s, 3H), -0.05 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7 (C), 144.1 (CH), 138.5 (C), 133.3 (C), 109.3 (C), 60.1 (CH_3), 54.7 (CH_2), 39.4 (CH), 36.0 (CH_2), 29.6 (CH_2), 29.0 (CH_3), 28.3 (CH), 11.14 (CH_2), -1.2 (CH_3), - 2.1 (CH_3).

HRMS (ESI+) calculated for $C_{15}H_{23}NO_2SiNa$ $[M+Na]^+$: 300.1399, found: 300.1408.

3-Methoxyprop-1-yne: (2.37)



C_4H_6O

To a mixture of 2-propynol **2.12** (6.0 g, 6.18 mL, 107.03 mmol) and water (4.65 mL) was added a 50% aqueous solution of NaOH (w/v; 12.85 g, 221.09 mmol). The reaction mixture was stirred for 30 minutes and dimethyl sulfate (8.03 g, 5.86 mL, 63.65 mmol) was added dropwise, the temperature was kept below 60 °C. After stirring at 50-60 °C for 2 hours, micro distillation gave a product that came over 61-62 °C, which was subsequently dried ($CaCl_2$) overnight. Finally, re-distillation of the product at atmospheric pressure using a cooled receiver afforded 7.50 g of the title compound **2.37** (80%) as a colourless oil.
Spectroscopic data are in agreement with the literature values.[198]

b.p.: 60 °C (760 Torr).

IR (neat) *v* (cm^{-1}) 3284, 2945, 2843, 2129, 1453, 1338, 1306, 1105.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (s, 2H), 3.30 (s, 3H), 2.40 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 79.4 (C), 77.3 (CH), 59.4 (CH_2), 57.2 (CH_3).

m/z (EI+) 31, 39, 69, 71.

4-Methoxybut-2-yn-1-ol: (2.38)

$C_5H_8O_2$

To a stirred solution of methyl ether **2.37** (4.0 g, 57.10 mmol) in dry THF (60 mL) at -78 ºC was added *n*-BuLi (2.3 M solution in hexanes, 26.07 mL, 59.95 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of powdered paraformaldehyde (5.14 g, 171.30 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched at 0 °C with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a pale yellow liquid. Distillation under reduced pressure afforded 4.91 g (86%) of clear colourless liquid. Spectroscopic data are in agreement with the literature values.[218]

b.p.: 96 – 97 °C (15 Torr).

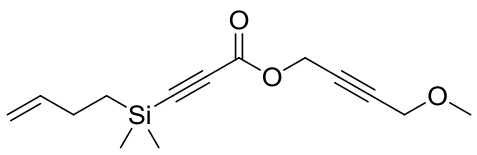
IR (neat) *v* (cm^{-1}) 3374, 2938, 2828, 1450, 1356, 1119, 1087, 1011, 894.

^1H NMR (500 MHz, $CDCl_3$) δ 4.22 (s, 2H), 4.0 5 (s, 2H), 3.38 (s, 3H), 3.0 (br s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 84.9 (C), 81.1 (C), 59.8 (CH_2), 57.2 (CH_3), 50.5 (CH_2).

HRMS (ESI+) calculated for $C_5H_8O_2Na$ $[M+Na]^+$: 123.0422, found: 123.0409.

4-Methoxybut-2-yn-1-yl 3-(but-3-en-1-yldimethylsilyl)propiolate: (2.35)



$C_{14}H_{20}O_3Si$

To a stirred solution of carboxylic acid **2.4** (2.0 g, 10.97 mmol) and 4 drops of DMF in dry CH_2Cl_2 (20 mL) at 0 °C was added oxalyl chloride (1.46 g, 0.98 mL, 11.52 mmol). The solution was allowed to warm to rt and left to stir for 2 hours. This was added to a solution of propargylic alcohol **2.38** (1.65 g, 16.45 mmol) and 2,6-lutidine (3.53 g, 3.81 mL, 32.91 mmol) in dry CH_2Cl_2 (40 mL) which had been stirring for 30 minutes. The resultant cloudy solution was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched with water, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.35** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.35** (2.15 g, 74%) as a yellow oil.

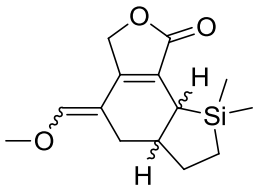
IR (neat) ν (cm^{-1}) 2926, 2850, 1715, 1436, 1366, 1252, 1134, 1023, 1097.

^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddt, J = 16.6, 10.1, 6.2 Hz, 1H), 5.03 (dd, J = 17.1, 1.6 Hz, 1H), 4.94 (dd, J = 10.1, 1.2 Hz, 1H), 4.80 (s, 2H), 4.13 (s, 2H), 3.38 (s, 3H), 2.19 – 2.13 (m, 2H), 0.83 – 0.78 (m, 2H), 0.25 (s, 3H), 0.23 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.0 (C), 140.3 (CH), 113.5 (CH_2), 94.5 (C), 94.3 (C), 83.5 (C), 79.4 (C), 59.7 (CH_2), 57.6 (CH_3), 53.4 (CH_2), 27.5 (CH_2), 14.3 (CH_2), -0.9 (CH_3), -2.4 (CH_3).

HRMS (ESI+) calculated for $C_{14}H_{20}O_3SiNa$ $[M+Na]^+$: 287.1100, found: 287.1074.

5-(Methoxymethylene)-1,1-dimethyl-3,3a,4,5,6,8b-hexahydro-*1H*-silolo[2,3-e]isobenzofuran-8(*2H*)-one: (2.39)



$C_{14}H_{20}O_3Si$

A solution of 4-methoxybut-2-yn-1-yl 3-(but-3-en-1-yldimethylsilyl) propiolate **2.35** (0.5 g, 1.89 mmol) in de-gassed toluene (189 mL) was heated at reflux for 20 hours. After cooling to rt the solvent was removed *in vacuo* and the crude product **2.39** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.39** (0.2 g, 40% isomer A+B, combined yield) as a yellow oil.

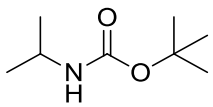
IR (neat) *v* (cm^{-1}) 2931, 2859, 1738, 1644, 1449, 1339, 1246, 1215, 1133, 1067, 1017, 976, 838, 796, 770, 752, 725, 618.

^{1}H NMR (500 MHz, $CDCl_3$) *Isomer A;* δ 6.05 (s, 1H), 5.06 – 4.92 (m, 2H), 3.68 (s, 3H), 2.37 – 2.35 (m, 1H), 2.11 – 1.07 (m, 5H), 0.92 – 0.58 (m, 2H), 0.30 (s, 3H), -0.03 (s, 3H); *Isomer B;* δ 6.11 (s, 1H), 5.06 – 4.92 (m, 2H), 3.69 (s, 3H), 2.44 (app. dd, *J* = 14.0, 3.0 Hz, 1H), 2.11 – 1.07 (m, 5H), 0.92 – 0.58 (m, 2H), 0.39 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) *Isomer A*; δ 174.6 (C), 148.9 (C), 147.1 (CH), 126.1 (C), 109.3 (C), 71.9 (CH_2), 60.5 (CH_3), 39.3 (CH), 32.9 (CH_2), 29.1 (CH_2), 27.5 (CH), 11.0 (CH_2), - 1.2 (CH_3), - 2.3 (CH_3); *Isomer B*; δ 174.4 (C), 154.3 (C), 148.2 (CH), 125.3 (C), 107.8 (C), 72.2 (CH_2), 60.6 (CH_3), 43.6 (CH), 30.5 (CH_2), 30.3 (CH), 30.2 (CH_2), 11.5 (CH_2), - 1.4 (CH_3), - 3.3 (CH_3).

HRMS (ESI+) calculated for $C_{14}H_{21}O_3Si$ $[M+H]^+$: 265.1200, found: 265.1249.

tert-Butyl isopropylcarbamate: (2.48)



$C_8H_{17}NO_2$

To a stirred solution of di-*tert*-butyl dicarbonate (24.0 g, 110 mmol) in dry THF (200 mL) at 0 °C was added isopropylamine **2.47** (5.91 g, 8.59 mL, 100 mmol). A catalytic amount of *N*,*N*-dimethylpyridin-4-amine (DMAP; 122 mg, 1 mmol) was then added and the reaction was left to stir at rt for 16 hours. Subsequently, the solvent was evaporated off under reduced pressure to give a yellow solid which was redissolved in diethyl ether (100 mL). The resultant solution was washed once with water, washed once with saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow tinted solid. The crude product **2.48** was purified by flash chromatography on a silica gel column eluting with 20% ethyl acetate in hexanes to give the title compound **2.48** (11.30 g, 71%) as a white solid.
Spectroscopic data are in agreement with the literature values.[200]

m.p.: 70 – 72 °C

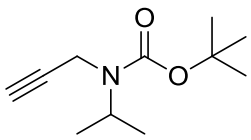
IR (neat) ν (cm^{-1}) 3342, 2974, 2932, 1679, 1528, 1455, 1363, 1248, 1168, 1076, 939, 886, 839, 776, 754.

^1H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 4.34 (br s, 1H), 3.75 (br s, 1H), 1.44 (s, 9H), 1.05 (d, J = 6.5 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1 (C), 78.9 (C), 42.5 (CH), 28.4 (CH_3), 23.0 (CH_3).

HRMS (ESI+) calculated for $C_8H_{17}NO_2Na$ $[M+Na]^+$: 182.1151, found: 182.1152.

tert-Butyl isopropyl(prop-2-yn-1-yl)carbamate: (2.50)



$C_{11}H_{19}NO_2$

To a stirred suspension of sodium hydride (60% *w/w* in mineral oil; 2.49 g, 62.17 mmol) in dry DMF (50 mL) was added *tert*-butyl isopropylcarbamate **2.48** (9.0 g, 56.52 mmol) in dry DMF (25 mL). The resultant solution was cooled to 0 °C before the addition of propargyl bromide **2.49** (7.39 g, 5.52 mL, 62.17 mmol). The reaction mixture was then allowed to warm to rt and left to stir for 16 hours. Subsequently, it was added to a stirring biphasic mixture of 10% aqueous K_2CO_3 solution and diethyl ether. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic layers were combined, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.50** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.50** (8.09 g, 66%) as a yellow oil.

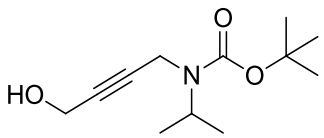
IR (neat) *v* (cm^{-1}) 3309, 2978, 2934, 2195, 1688, 1443, 1402, 1365, 1329, 1271, 1250, 1214, 1162, 1097, 1070, 943, 898, 861, 774, 748.

^1H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 4.20 (br s, 1H), 3.80 (s, 2H), 2.09 (s, 1H), 1.43 (s, 9H), 1.15 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6 (C), 85.0 (C), 79.8 (C), 68.9 (CH), 47.6 (CH), 31.1 (CH_2), 28.3 (CH_3), 20.4 (CH_3).

HRMS (ESI+) calculated for $C_{11}H_{20}NO_2$ $[M+H]^+$: 198.1489, found: 198.1493.

tert-Butyl (4-hydroxybut-2-yn-1-yl)(isopropyl)carbamate: (2.51)



$C_{12}H_{21}NO_3$

To a stirred solution of alkyne **2.50** (6.0 g, 30.41 mmol) in dry THF (118 mL) at -78 ºC was added *n*-BuLi (2.5 M solution in hexanes, 12.77 mL, 31.93 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of powdered paraformaldehyde (1.82 g, 60.82 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction mixture was then quenched at 0 °C with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a dark yellow liquid. The crude product **2.51** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.51** (5.59 g, 81%) as a yellow oil.

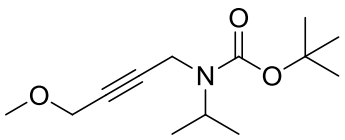
IR (neat) *v* (cm^{-1}) 3416, 2975, 2932, 1669, 1443, 1404, 1365, 1332, 1272, 1252, 1161, 1128, 1102, 1065, 1018, 939, 898, 862.

^1H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 4.20 (br s, 3H), 3.80 (s, 2H), 2.60 (br s, 1H), 1.40 (s, 9H), 1.18 (d, *J* = 6.7 Hz, 6H).

13C NMR (126 MHz, $CDCl_3$) δ 155.7 (C), 82.0 (C), 80.0 (C), 79.9 (C), 51.0 (CH_2), 47.5 (CH), 31.5 (CH_2), 28.4 (CH_3), 20.5 (CH_3).

HRMS (ESI+) calculated for $C_{12}H_{21}O_3NNa$ $[M+Na]^+$: 250.1414, found: 250.1415.

tert-Butyl isopropyl(4-methoxybut-2-yn-1-yl)carbamate: (2.52)



$C_{13}H_{23}NO_3$

To dimethyl sulfoxide (35 mL) was added powder potassium hydroxide (3.24 g, 57.69 mmol). After stirring the suspension for 5 minutes a solution of propargylic alcohol **2.51** (4.0 g, 14.42 mmol) in dimethyl sulfoxide (15 mL) was added, followed by immediate addition of methyl iodide (4.09 g, 1.79 ml, 28.85 mmol). The resultant solution was left to stir at rt for 16 hours. Subsequently, the reaction mixture was quenched with water. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a dark yellow oil. The crude product **2.52** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.52** (2.99 g, 86%) as a yellow oil.

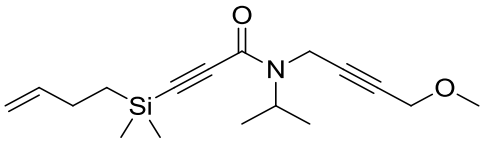
IR (neat) ν (cm^{-1}) 2976, 2933, 1690, 1443, 1401, 1365, 1330, 1271, 1251, 1213, 1162, 1125, 1093, 1065, 1002, 941, 901, 863.

^1H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 4.20 (br s, 1H), 4.05 (s, 2H), 3.92 (br s, 2H), 3.33 (s, 3H), 1.45 (s, 9H), 1.17 (d, J = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7 (C), 84.3 (C), 79.7 (C), 77.4 (C), 59.9 (CH_2), 57.2 (CH_3), 47.3 (CH), 31.7 (CH_2), 28.4 (CH_3), 20.5 (CH_3).

HRMS (ESI+) calculated for $C_{13}H_{23}NO_3Na$ $[M+Na]^+$: 264.1627, found: 264.1632.

3-(But-3-en-1-yldimethylsilyl)-*N*-isopropyl-*N*-(4-methoxybut-2-yn-1-yl)propiolamide: (2.46)



$C_{17}H_{27}NO_2Si$

To a stirred solution of *N*-Boc amine **2.52** (2.6 g, 10.77 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added a 4.0 M solution of HCl in dioxane (64.62 mL, 258.48 mmol). The reaction was allowed to warm to rt and left to stir for 4 hours, during which time the formation of brown precipitates were observed. The solvent was removed *in vacuo* to afford a pale brown solid. This solid was triturated with diethyl ether to afford a dark brown solid which was collected by filtration and washed well with diethyl ether, after drying under high vacuum the title product obtained was a brown solid. The crude product **2.53** was used directly in the next step without future purifications (2.47, 74%).

To a stirred solution of carboxylic acid **2.4** (1.78 g, 9.75 mmol) and 4 drops of DMF in dry CH_2Cl_2 (40 mL) at 0 °C was added oxalyl chloride (1.30 g, 0.88 mL, 10.24 mmol). The solution was allowed to warm to rt and left to stir for 2 hours. This was added to a solution of propargylic amine **2.53** (2.6 g, 14.63 mmol) and 2,6-lutidine (3.13 g, 3.39 mL, 29.25 mmol) in dry CH_2Cl_2 (20 mL) which had been stirring for 30 minutes. The resultant cloudy solution was allowed to warm to rt and left to stir for 16 hours. The reaction mixture was then quenched with water. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.46** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.46** (2.08 g, 70%) as a yellow oil.

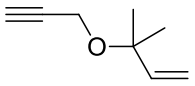
IR (neat) ν (cm^{-1}) 2972, 2950, 2923, 2249, 1685, 1636, 1409, 1365, 1331, 1249, 1201, 1187, 1128, 1097, 1077, 1059, 906, 843

^{1}H NMR (500 MHz, $CDCl_3$, resolved signals of rotamers) *Rotamer A:* δ 5.87 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 1H), 5.01 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.92 (dd, *J* = 10.1, 1.0 Hz, 1H), 4.72 – 4.62 (m, 1H), 4.11 (s, 1H), 4.05 (s, 1H), 3.33 (s, 1.5H), 2.20 – 2.12 (m, 2H), 1.31 (d, *J* = 6.8 Hz, 3H), 0.81 – 0.77 (m, 2H), 0.23 (s, 3H), 0.22 (s, 3H); *Rotamer B:* δ 4.29 (s, 1H), 4.08 (br s, 1H), 3.35 (app. d, *J* = 3.9 Hz, 1.5H), 1.23 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, resolved signals of rotamers) *Rotamer A*: δ 153.2 (C), 140.5 (CH), 113.4 (CH_2), 97.0 (C), 96.2 (C), 82.5 (C), 78.1 (C), 59.8 (CH_2), 57.4 (CH_3), 50.6 (CH), 29.1 (CH_2), 27.7 (CH_2), 20.9 (CH_3), 14.6 (CH_2), - 0.7 (CH_3), - 2.2 (CH_3); *Rotamer B*: 153.5 (C), 140.6 (CH), 113.3 (CH_2), 97.0 (C), 96.0 (C), 82.6 (C), 79.3 (C), 59.7 (CH_2), 45.6 (CH), 34.2 (CH_2), 27.6 (CH_2), 19.9 (CH_3).

HRMS (ESI+) calculated for $C_{17}H_{27}NO_2SiNa$ $[M+Na]^+$: 328.1722, found: 328.1714.

3-Methyl-3-(prop-2-yn-1-yloxy)but-1-ene: (2.62)



$C_8H_{12}O$

To a stirred suspension of sodium hydride (60% *w/w* in mineral oil; 5.57 g, 139.32 mmol) in dry THF (100 mL) was added 2-methylbut-3-en-2-ol **2.61** (10.0 g, 116.10 mmol) in dry THF (20 mL). The resultant solution was cooled to 0 °C before the addition of propargyl bromide **2.49** (13.81, 10.31 mL, 116.10 mmol). The reaction mixture was then allowed to warm to rt and left to stir for 16 hours. Subsequently, it was added to a stirring biphasic mixture of 10% aqueous K_2CO_3 solution and diethyl ether. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a brown liquid. The crude product **2.62** was

purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.62** (9.37 g, 65%) as a brown oil.

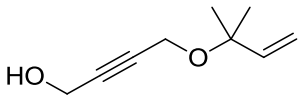
IR (neat) *v* (cm^{-1}) 3306, 2980, 2927, 2857, 1640, 1414, 1377, 1362, 1147, 1061, 1002, 925, 871, 657, 625.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.20 (d, *J* = 7.4 Hz, 1H), 5.17 (s, 1H), 4.00 (d, *J* = 2.3 Hz, 2H), 2.38 (t, *J* = 2.2 Hz, 1H), 1.33 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7 (CH), 114.7 (CH_2), 81.5 (C), 76.6 (C), 73.0 (CH), 51.1 (CH_2), 25.7 (CH_3).

Ion not found

4-((2-Methylbut-3-en-2-yl)oxy)but-2-yn-1-ol: (2.63)



$C_9H_{14}O_2$

To a stirred solution of alkyne **2.62** (4.0 g, 32.21 mmol) in dry THF (60 mL) at -78 ºC was added *n*-BuLi (2.4 M solution in hexanes, 14.09 mL, 33.82 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of powdered paraformaldehyde (1.93 g, 64.42 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched at 0 °C with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow liquid.

The crude product **2.63** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.63** (4.02 g, 81%) as a yellow oil.

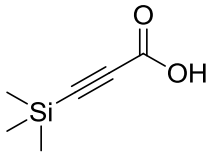
IR (neat) *v* (cm^{-1}) 3394, 2979, 2931, 2865, 1640, 1414, 1377, 1361, 1206, 1136, 1003, 926, 878, 836, 690.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (dd, *J* = 17.8, 10.7 Hz, 1H), 5.19 (d, *J* = 4.8 Hz, 1H), 5.16 (s, 1H), 4.30 (s, 2H), 4.03 (s, 2H), 1.32 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7 (CH), 114.8 (CH_2), 83.3 (C), 83.2 (C), 76.4 (C), 51.35 (CH_2), 51.2 (CH_2), 25.7 (CH_3).

HRMS (ESI+) calculated for $C_9H_{14}O_2Na$ $[M+Na]^+$: 177.0886, found: 177.0883.

3-(Trimethylsilyl)propiolic acid: (2.65)



$C_6H_{10}O_2Si$

To a stirred solution of ethynyltrimethylsilane **2.64** (12.5 g, 17.98 mL, 127.0 mmol) in dry diethyl ether (50 mL) at -78 ºC was added MeLi (1.6 M solution in hexanes, 83.34 mL, 133.35 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of previously crushed solid CO_2 pellets (50 g) *via* the side-arm solid addition funnel. The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction mixture was then quenched at 0 °C with 1.0 M aqueous HCl solution. The phases were separated and the aqueous phase was extracted

three times with diethyl ether. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellowish liquid. The residue was purified *via* short-path distillation to give the title compound **2.65** as a clear colourless oil (15.89 g, 88%).

b.p.: 62 °C (0.2 Torr).

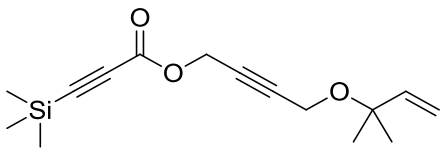
IR (neat) *v* (cm^{-1}) 2965, 2904, 2626, 2178, 1694, 1517, 1404, 1254, 921, 847.

^{1}H (500 MHz, $CDCl_3$, broadened signals were observed) δ 11.36 (br s, 1H), 0.24 (s, 9H).

^{13}C (126 MHz, $CDCl_3$) δ 157.8 (C), 97.4 (C), 93.7 (C), -1.1 (CH_3).

m/z (EI+) 127, 99, 83.

4-((2-Methylbut-3-en-2-yl)oxy)but-2-yn-1-yl 3-(trimethylsilyl)propiolate: (2.60)



$C_{15}H_{22}O_3Si$

To a stirred solution of 3-(trimethylsilyl)propiolic acid **2.65** (2.0 g, 10.97 mmol) and 4 drops of DMF in dry CH_2Cl_2 (30 mL) at 0 °C was added oxalyl chloride (1.46 g, 0.98 mL, 11.52 mmol). The solution was allowed to warm to rt and left to stir for 2 hours. This was added to a solution of propargylic alcohol **2.63** (2.5 g, 16.45 mmol) and 2,6-lutidine (3.53 g, 3.81 mL, 32.91 mmol) in dry CH_2Cl_2 (15 mL) which had been stirring for 30 minutes. The resultant cloudy solution was allowed to warm to rt and left to stir for 16 hours. The reaction mixture was then quenched with water. The phases were separated and the aqueous phase was

extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.60** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.60** (2.15 g, 74%) as a yellow oil.

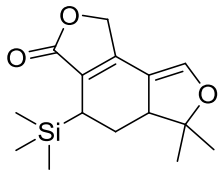
IR (neat) *v* (cm^{-1}) 2977, 2898, 2857, 2175, 1716, 1414, 1365, 1252, 1144, 1204, 1057, 1002, 929, 842, 760, 751.

^1H NMR (400 MHz, $CDCl_3$) δ 5.88 – 5.79 (m, 2H), 5.21 (d, *J* = 1.0 Hz, 1H), 5.17 (d, *J* = 4.2 Hz, 1H), 4.81 (s, 2H), 4.05 (s, 2H), 1.33 (s, 6H), 0.26 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.1 (C), 142.6 (CH), 114.9 (CH_2), 95.3 (C), 93.7 (C), 85.3 (C), 77.9 (C), 76.5 (C), 53.7 (CH_2), 51.3 (CH_2), 25.7 (CH_3), -0.9 (CH_3).

HRMS (ESI+) calculated for $C_{15}H_{22}O_3SiNa$ $[M+Na]^+$: 301.1236, found: 301.1250.

6,6-dimethyl-4-(trimethylsilyl)-4,5,5a,6-tetrahydrobenzo[1,2-c:3,4-c']difuran-3(1H)-one (2.66)



$C_{15}H_{22}O_3Si$

A solution of 4-((2-methylbut-3-en-2-yl)oxy)but-2-yn-1-yl 3-(trimethylsilyl)propiolate **2.60** (450 mg, 1.62 mmol) in de-gassed toluene (16.2 mL) was heated at reflux for 1 hour. After cooling to rt the solvent was removed *in vacuo* and the crude product was purified by flash

chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.66** (432 mg, 96%) as a yellow oil.

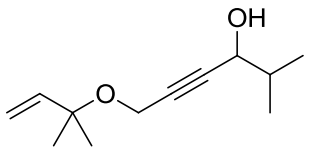
IR (neat) *v* (cm^{-1}) 2959, 2927, 2874, 1737, 1629, 1457, 1348, 1246, 1157, 1136, 1089, 1065, 1032, 905, 835, 808, 766, 743.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (s, 1H), 4.88 (s, 2H), 2.89 (d, *J* = 13.0 Hz, 1H), 2.26 (d, *J* = 5.4 Hz, 1H), 1.94 (dd, *J* = 12.3, 4.1 Hz, 1H), 1.69 – 1.60 (m, 1H), 1.56 (s, 3H), 1.15 (s, 3H), 0.09 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4 (C), 147.6 (C), 141.5 (CH), 124.0 (C), 110.6 (C), 90.4 (C), 68.4 (CH_2), 48.3 (CH), 27.9 (CH_3), 24.2 (CH_2), 23.5 (CH), 21.7 (CH_3), -1.2 (CH_3).

HRMS (ESI+) calculated for $C_{15}H_{23}O_3Si$ $[M+H]^+$: 279.1416, found: 279.1431.

2-Methyl-6-((2-methylbut-3-en-2-yl)oxy)hex-4-yn-3-ol: (2.69)



$C_{12}H_{20}O_2$

To a stirred solution of alkyne **2.62** (4.0 g, 32.21 mmol) in dry THF (60 mL) at -78 ºC was added *n*-BuLi (2.5 M solution in hexanes, 13.52 mL, 33.82 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of *iso*-butyraldehyde (4.44 g, 3.09 ml, 33.82 mmol). The reaction mixture was allowed to warm to rt and left to stir for 8 hours. The reaction was then quenched at 0 °C with water. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with brine, dried over

anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow liquid. The crude product **2.69** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.69** (6.07 g, 96%) as a yellow oil.

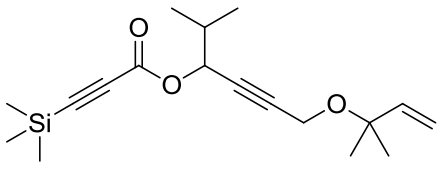
IR (neat) *v* (cm^{-1}) 3413, 2975, 2872, 1467, 1414, 1377, 1255, 1144, 1109, 1030, 1001, 925, 880, 838, 690.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.15 (d, *J* = 9.3 Hz, 1H), 5.12 (s, 1H), 4.16 (d, *J* = 3.8 Hz, 1H), 4.01 (s, 2H), 1.88 – 1.78 (m, 1H), 1.28 (s, 6H), 0.98 – 0.94 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.9 (CH), 114.5 (CH_2), 84.8 (C) 83.1 (C), 76.5 (C), 67.8 (CH), 51.3 (CH_2), 34.3 (CH), 25.8 (CH_3), 25.7 (CH_3), 18.0 (CH_3), 17.5 (CH_3).

HRMS (ESI+) calculated for $C_{12}H_{20}O_2Na$ $[M+Na]^+$: 219.1356, found: 219.1352.

2-Methyl-6-((2-methylbut-3-en-2-yl)oxy)hex-4-yn-3-yl 3-(trimethylsilyl)propiolate: (2.67)



$C_{18}H_{28}O_3Si$

To a stirred solution of 3-(trimethylsilyl)propiolic acid **2.65** (1.69 g, 11.89 mmol) and 4 drops of DMF in dry CH_2Cl_2 (40 mL) at 0 °C was added oxalyl chloride (1.58 g, 1.07 mL, 12.48 mmol). The solution was allowed to warm to rt and left to stir for 2 hours. This was added to a solution of propargylic alcohol **2.69** (3.5 g, 17.83 mmol) and 2,6-lutidine (3.53 g, 3.81 mL, 32.91 mmol) in dry CH_2Cl_2 (20 mL) which had been stirring for 30 minutes. The resulting

cloudy solution was then allowed to warm to rt and left to stir for 16 hours. Subsequently, the reaction mixture was quenched with water. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.67** was purified by flash chromatography on a silica gel column eluting with 15% diethyl ether in hexanes to give the title compound **2.67** (2.15 g, 74%) as a yellow oil.

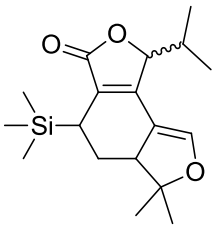
IR (neat) *v* (cm^{-1}) 2969, 2938, 2905, 2178, 1713, 1469, 1414, 1377, 1360, 1333, 1253, 1212, 1147, 1079, 1057, 987, 931, 910, 842, 761, 750.

^{1}H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 5.81 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.29 (dd, *J* = 5.7, 0.9 Hz, 1H), 5.16 (d, *J* = 8.3 Hz, 1H), 5.13 (br s, 1H), 4.03 (s, 2H), 2.07 – 1.97 (m, 1H), 1.29 (s, 6H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.23 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.0 (C), 142.92(CH), 114.64(CH_2), 94.5 (C), 94.2 (C), 84.8 (C), 79.9 (C), 76.5 (C), 70.7 (CH), 51.3 (CH_2), 32.3 (CH), 25.8 (CH_3), 25.7 (CH_3), 18.1 (CH_3), 17.5 (CH_3), -0.9 (CH_3).

HRMS (ESI+) calculated for $C_{18}H_{28}O_3SiNa$ $[M+Na]^+$: 343.1700, found: 343.1690.

1-isopropyl-6,6-dimethyl-4-(trimethylsilyl)-4,5,5a,6-tetrahydrobenzo[1,2-c:3,4-c']difuran-3(*1H*)-one: (2.70a-b)



$C_{18}H_{28}O_3Si$

A solution of 2-methyl-6-((2-methylbut-3-en-2-yl)oxy)hex-4-yn-3-yl-3-(trimethylsilyl) propiolate **2.67** (0.5 g, 1.56 mmol) in de-gassed toluene (15.6 mL) was heated at reflux for 30 minutes. After cooling to rt the solvent was removed *in vacuo* and the crude product was purified by flash chromatography on a silica gel column eluting with 40% diethyl ether in hexanes to give the title compound **2.70a-b** (475 mg, 95% diastereoisomer A+B, combined yield) as a yellow oil.

Diastereoisomer A:

Rf (hexane/Et_2O, 6/4) = 0.47

IR (neat) *v* (cm^{-1}) 2961, 2930, 1734, 1629, 1461, 1368, 1347, 1293, 1214, 1251, 1163, 1135, 1096, 1066, 1032, 1008, 955, 902, 834, 808, 753.

^1H NMR (500 MHz, $CDCl_3$) δ 6.55 (d, *J* = 2.0 Hz, 1H), 5.00 (d, *J* = 2.0 Hz, 1H), 2.88 (ddd, *J* = 13.4, 4.1, 2.3 Hz, 1H), 2.28 (d, *J* = 5.5 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.93 (dd, *J* = 12.3, 4.2 Hz, 1H),, 1.62 – 1.57 (m, 1H), 1.55 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.13 (s, 3H), 0.68 (d, *J* = 6.8 Hz, 3H), 0.09 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1 (C), 149.7 (C), 141.6 (CH), 125.3 (C), 110.7 (C), 90.0 (C), 84.2 (CH), 48.8 (CH), 31.9 (CH), 27.6 (CH_3), 24.2 (CH_2), 23.4 (CH), 21.4 (CH_3), 19.9 (CH_3), 13.2 (CH_3), -1.2 (CH_3).

Diastereoisomer B:

Rf (hexane/Et_2O, 6/4) = 0.38

IR (neat) *v* (cm^{-1}) 2963, 2926, 1729, 1630, 1462, 1384, 1371, 1299, 1247, 1216, 1160, 1137, 1091, 1066, 1036, 1003, 958, 900, 837, 809, 771.

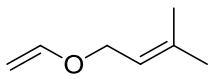
^1H NMR (500 MHz, $CDCl_3$) δ 6.51 (d, *J* = 2.0 Hz, 1H), 4.95 (t, *J* = 2.5 Hz, 1H), 2.88 (ddd, *J* = 13.3, 4.2, 2.2 Hz, 1H), 2.25 (d, *J* = 6.0 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.93 (dd, *J* = 12.4, 4.2

Hz, 1H), 1.67 – 1.60 (m, 1H), 1.56 (s, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.14 (s, 3H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.10 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3 (C), 150.0 (C), 141.8 (CH), 124.9 (C), 110.8 (C), 90.2 (C), 84.3 (CH), 48.3 (CH), 31.7 (CH), 27.9 (CH_3), 24.2 (CH_2), 23.4 (CH), 21.8 (CH_3), 19.7 (CH_3), 14.5 (CH_3), -1.0 (CH_3).

HRMS (ESI+) calculated for $C_{18}H_{29}O_2Si$ $[M+H]^+$: 321.1880, found: 321.1882.

3-Methyl-1-(vinyloxy)but-2-ene: (2.73)



$C_7H_{12}O$

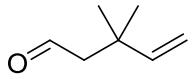
To a solution of 3-methyl-2-buten-ol **2.71** (10.0 g, 0.116 mol) in ethyl vinyl ether (111 mL, 1.16 mol), mecury(II) acetate (37.0 g, 0.116 mol) was added.. The resulting mixture was stirred at room temperature for 2 days. After that, the reaction mixture was washed with water and brine. The organic layer dried by anhydrous $MgSO_4$ and evaporated. The residue oil was filtered *via* a short silica gel column that was then washed with copious compatible eluent. The filtrate was concentrated and distilled under reduced pressure to give the desire compound **2.73** as a colourless liquid (8.58 g, 66%).
Spectroscopic data are in agreement with the literature values [206]

b.p.: 114 - 115 °C (760 Torr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 14.2, 6.8 Hz, 1H), 5.50 – 5.30 (m, 1H), 4.34 – 4.16 (m, 3H), 3.99 (dd, *J* = 6.8, 1.7 Hz, 1H), 1.77 (s, 3H), 1.70 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.6 (CH), 137.9 (C), 119.5 (CH), 86.6 (CH_2), 64.8 (CH_2), 25.7 (CH_3), 18.0 (CH_3).

3,3-Dimethylpent-4-enal: (2.74)



$C_7H_{12}O$

The 3-methyl-1-(vinyloxy)but-2-ene **2.73** (7.3 g, 65 mmol) was heated at reflux under argon for 24 hours and cooled to rt to obtain the pure title aldehyde **2.74** (7.08 g, 97%). The temperature of the reaction mixture increased gradually during the reflux period and reached 141 °C, a constant temperature after 20 hours.
Spectroscopic data are in agreement with the literature values.[219]

b.p.: 53 - 54 °C (55 Torr).

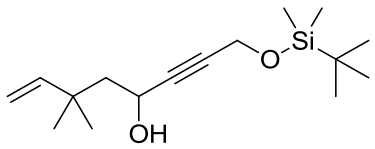
IR (neat) *v* (cm^{-1}) 3086, 2964, 2736, 1720, 1649, 1469, 1413, 1366, 1161, 1040, 1001, 915, 682.

^{1}H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 9.68 (t, *J* = 3.1 Hz, 1H), 5.88 (dd, *J* = 15.6, 10.7, 1H), 5.00 (br s, 1H), 4.99 (d, *J* = 4.0 Hz, 1H), 2.33 (d, *J* = 3.1 Hz, 2H), 1.12 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9 (CH), 146.2 (CH), 111.7 (CH_2), 54.5 (CH_2), 35.8 (C), 27.2 (CH_3).

HRMS (ESI+) calculated for $C_{14}H_{25}O_2$ $[2M+H]^+$: 225.1849, found: 225.1858.

1-((*tert*-Butyldimethylsilyl)oxy)-6,6-dimethyloct-7-en-2-yn-4-ol: (2.75)



$C_{16}H_{30}O_2Si$

To a stirred solution of *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane **2.16** (9.4 g, 55.19 mmol) in dry THF (125 mL) at -78 ºC was added *n*-BuLi (2.3 M solution in hexanes, 25.19 mL, 57.95 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of 3,3-dimethylpent-4-enal **2.74** (6.5 g, 57.95 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched at 0 °C with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellowish liquid. The crude product **2.75** was purified by flash chromatography on a silica gel column eluting with 15% diethyl ether in hexanes to give the title compound **2.75** (14.5 g, 93%) as a pale yellow oil.

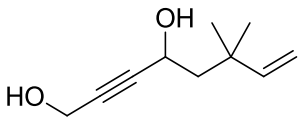
IR (neat) *v* (cm^{-1}) 3369, 2957, 2930, 2859, 1640, 1464, 1412, 1365, 1254, 1123, 1080, 1000, 912, 777, 726.

^{1}H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 5.87 (dd, *J* = 17.5, 10.8 Hz, 1H), 4.99 (dd, *J* = 9.4, 1.1 Hz, 1H), 4.97 (d, *J* = 1.3 Hz, 1H), 4.44 (br s, 1H), 4.33 (s, 2H), 1.91 (br s, 1H, OH), 1.81 –1.76 (m, 2H), 1.09 (s, 3H), 1.08 (s, 3H), 0.91 (s, 9H), 0.12 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8 (CH), 111.2 (CH_2), 86.6 (C), 83.2 (C), 60.2 (CH), 51.7 (CH_2), 50.3 (CH_2), 36.1 (C), 27.7 (CH_3), 26.5 (CH_3), 25.8 (CH_3), 18.26 (C), -5.14 (CH_3).

HRMS (ESI+) calculated for $C_{16}H_{30}O_2SiNa$ $[M+Na]^+$: 305.1907, found: 305.1901.

6,6-Dimethyloct-7-en-2-yne-1,4-diol: (2.76)



$C_{10}H_{16}O_2$

To a stirred solution of TBS-protected alkyl silyl ether **2.75** (13.0 g, 46.02 mmol) in dry THF (25 mL) was added a 1.0 M solution of TBAF in THF (55.2 mL, 55.2 mmol). After stirring for 2 hours the reaction was concentrated under reduced pressure. The crude product **2.76** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.76** (7.35 g, 95%) as a pale yellow oil.

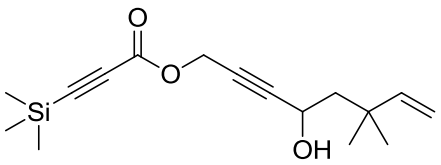
IR (neat) *v* (cm^{-1}) 3315, 2957, 2867, 1640, 1414, 1365, 1303, 1121, 1013, 909, 685.

^1H NMR (500 MHz, $CDCl_3$, broadened signals were observed) δ 5.87 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.03 – 5.00 (m, 1H), 4.99 (br s, 1H), 4.47 (br s, 1H), 4.29 (s, 2H), 2.32 (br s, 2H, OH), 1.87 – 1.75 (m, 2H), 1.10 (s, 3H), 1.09 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8 (CH), 111.4 (CH_2), 87.6 (C), 82.8 (C), 60.2 (CH), 50.9 (CH_2), 50.3 (CH_2), 36.1 (C), 27.8 (CH_3), 26.5 (CH_3).

HRMS (ESI) calculated for $C_{10}H_{18}O_3[M+H_2O]^+$: 186.1494, found 186.2098

4-Hydroxy-6,6-dimethyloct-7-en-2-yn-1-yl 3-(trimethylsilyl)propiolate: (2.77)



$C_{16}H_{24}O_3Si$

To a stirred solution of 3-(trimethylsilyl)propiolic acid **2.65** (3.95 g, 27.74 mmol) and 4 drops of DMF in dry CH_2Cl_2 (50 mL) at 0 °C was added oxalyl chloride (3.7 g, 2.5 mL, 29.13 mmol). The solution was allowed to warm to rt and left to stir for 2 hours. This was added to a solution of propargylic alcohol **2.76** (7.0 g, 41.61 mmol) and 2,6-lutidine (8.92 g, 9.64 mL, 83.22 mmol) in dry CH_2Cl_2 (30 mL) which had been stirring for 30 minutes. The resultant cloudy solution was then allowed to warm to rt and left to stir for 16 hours. Subsequently the reaction mixture was quenched with water. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.77** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.77** (5.68 g, 70%) as a yellow oil.

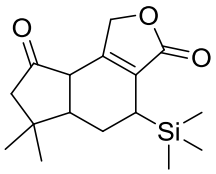
IR (neat) *v* (cm^{-1}) 3409, 2962, 2173, 1716, 1640, 1414, 1367, 1252, 1203, 1134, 1043, 999, 914, 842, 760, 703.

^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.01 (dd, *J* = 6.3, 0.9 Hz, 1H), 4.98 (br s, 1H), 4.77 (d, *J* = 1.6 Hz, 2H), 4.46 (td, *J* = 5.3, 1.7 Hz, 1H), 1.94 (br s, 1H, OH), 1.85 – 1.74 (m, 2H), 1.10 (s, 3H), 1.09 (s, 3H), 0.25 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.1 (C), 147.6 (CH), 111.4 (CH_2), 95.4 (C), 93.7 (C), 89.4 (C), 77.5 (C), 60.1 (CH), 53.4 (CH_2), 50.0 (CH_2), 36.1 (C), 27.7 (CH_3), 26.5 (CH_3), -0.9 (CH_3)

HRMS (ESI) calculated for $C_{16}H_{25}O_3Si$ $[M+H]^+$ 293.1573, found 293.1579

6,6-dimethyl-4-(trimethylsilyl)-5,5a,6,7-tetrahydro-*1H*-indeno[4,5-c]furan-3,8(4H,8aH)-dione: (2.78)



$C_{16}H_{24}O_3Si$

A solution of 4-hydroxy-6,6-dimethyloct-7-en-2-yn-1-yl 3-(trimethylsilyl)propiolate **2.77** (500 mg, 1.71 mmol) in de-gassed toluene (171 mL) was heated at reflux for 4 hours. After cooling to rt the solvent was removed *in vacuo* and the crude product was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.78** (410 mg, 82%) as a yellow oil.

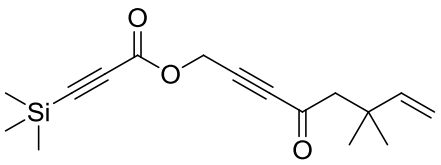
IR (neat) *v* (cm^{-1}) 2957, 2900, 2870, 1732, 1666, 1447, 1386, 1369, 1330, 1301, 1244, 1166, 1135, 1114, 1088, 1059, 1036, 1021, 999, 975, 840, 782.

^1H NMR (500 MHz, $CDCl_3$) δ 5.21 – 5.15 (m, 1H), 4.82 – 4.76 (m, 1H), 3.31 (d, *J* = 7.2 Hz, 1H,), 2.29 (d, *J* = 18.7 Hz, 1H, CH_2), 2.21 – 2.09 (m, 4H), 1.45 – 1.36 (m, 1H, CH_2), 1.21 (s, 3H), 1.19 (s, 3H), 0.10 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 213.6 (C), 172.9 (C), 151.7 (C), 130.1 (C), 71.3 (CH_2), 49.2 (CH), 48.4 (CH_2), 43.8 (CH), 36.9 (C), 29.8 (CH_3), 25.5 (CH_2), 24.5 (CH_3), 22.0 (CH), -1.1 (CH_3).

HRMS (ESI+) calculated for $C_{16}H_{24}O_3SiNa$ $[M+Na]^+$: 315.1567, found: 315.1387.

6,6-Dimethyl-4-oxooct-7-en-2-yn-1-yl 3-(trimethylsilyl)propiolate: (2.81)



$C_{16}H_{22}O_3Si$

To a stirred solution of alcohol **2.77** (2.0 g, 6.84 mmol) in acetone (15 mL) at 0 °C was slowly added Jones' reagent (3.0M solution, 6.84 mL, 20.52 mmol). The resultant mixture was stirred at 0 °C for 1 hour, it was then allowed to warm to rt and stirred for a further 3 hours. Subsequently, the reaction mixture was quenched with water, the phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow liquid. The crude product **2.81** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.81** (1.75 g, 88%) as a pale yellow oil.

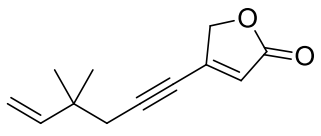
IR (neat) *v* (cm^{-1}) 2963, 2929, 2877, 2183, 1720, 1671, 1426, 1366, 1265, 1253, 1195, 1127, 916, 868, 843, 761, 681

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 17.3, 10.8 Hz, 1H), 4.99 (d, *J* = 7.2 Hz, 1H), 4.97 (br s, 1H), 4.88 (s, 2H), 2.59 (s, 2H), 1.15 (s, 6H), 0.27 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 185.4 (C), 151.7 (C), 146.2 (CH), 111.3 (CH_2), 96.4 (C), 93.2 (C), 86.8 (C), 83.6 (C), 56.5 (CH_2), 52.5 (CH_2), 36.9 (C), 26.9 (CH_3), -0.9 (CH_3).

HRMS (ESI+) calculated for $C_{16}H_{22}O_3SiNa$ $[M+Na]^+$: 313.1230, found: 313.1222.

4-(4,4-Dimethylhex-5-en-1-yn-1-yl)furan-2(*5H*)-one: (2.82)



$C_{12}H_{14}O_2$

A solution of 6,6-dimethyl-4-oxooct-7-en-2-yn-1-yl 3-(trimethylsilyl)propiolate **2.81** (0.5 g, 1.72 mmol) in de-gassed toluene (172 mL) was heated at reflux for 4 hours. After cooling to rt the solvent was removed *in vacuo* and the crude product was purified by flash chromatography on a silica gel column eluting with 10% diethyl ether in hexanes to give the title compound **2.82** (150 mg, 30%) as a yellow oil.

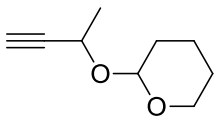
IR (neat) *v* (cm^{-1}) 2962, 2926, 2862, 2225, 1779, 1750, 1611, 1449, 1365, 1290, 1259, 1144, 1091, 1041, 1019, 909, 855, 798, 730.

^1H NMR (500 MHz, $CDCl_3$) δ 6.10 (s, 1H), 5.85 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.03 (d, *J* = 12.9 Hz, 1H), 5.01 (d, *J* = 6.2 Hz, 1H), 4.77 (d, *J* = 1.6 Hz, 2H), 2.45 (s, 2H), 1.14 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5 (C), 147.9 (C), 145.9 (CH), 121.5 (CH), 111.6 (CH_2), 105.8 (C), 73.1 (CH_2), 73.1 (C), 36.95 (C), 33.36 (CH_2), 26.52 (CH_3).

HRMS (ESI+) calculated for $C_{12}H_{14}O_2Na$ $[M+Na]^+$: 213.0886, found: 213.0884.

2-(But-3-yn-2-yloxy)tetrahydro-*2H*-pyran: (2.89)



$C_9H_{14}O_2$

To a stirred solution of 3,4-dihydro-*2H*-pyran (18.00 g, 19.52 mL, 214 mmol) and *para*-toluenesulphonic acid monohydrate (270 mg) in CH_2Cl_2 (175 mL) at 0 °C was added but-3-yn-2-ol **2.88** (10.0 g, 10.63 mL, 142.67 mmol). The reaction was allowed to warm to rt and left to stir for 4 hours. Subsequently, the solution was diluted with diethyl ether and washed once with half-saturated brine to remove the catalyst, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.89** was purified by flash chromatography on a silica gel column eluting with 5% ethyl acetate in pentane to give the title compound **2.89** (21.34 g, 97% diastereoisomers A+B, combined yield) as a pale yellow oil.
Spectroscopic data are in agreement with the literature values.[211]

Diastereoisomer A:

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (t, *J* = 3.2 Hz, 1H), 4.45 (qd, *J* = 6.5, 2.0 Hz, 1H), 4.02 – 3.97 (m, 1H), 3.56 – 3.50 (m, 1H), 2.42 (d, *J* = 2.0 Hz, 1H), 1.88 – 1.49 (m, 6H), 1.44 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 97.3 (CH), 84.9 (C), 72.3 (CH), 62.2 (CH), 62.1 (CH_2), 30.7 (CH_2), 25.5 (CH_2), 21.9 (CH_3), 19.2 (CH_2).

Diastereoisomer B:

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (t, *J* = 3.5 Hz, 1H), 4.56 (qd, *J* = 6.5, 2.0 Hz, 1H), 3.82 – 3.78 (m, 1H), 3.56 – 3.50 (m, 1H), 2.40 (d, *J* = 2.0 Hz, 1H), 1.88 – 1.49 (m, 6H), 1.47 (d, *J* = 6.6 Hz, 3H).

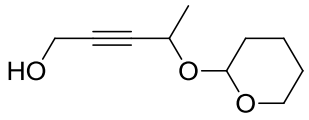
^{13}C NMR (126 MHz, $CDCl_3$) δ 96.0 (CH), 84.0 (C), 73.0 (CH), 62.5 (CH), 61.1 (CH_2), 30.7 (CH_2), 25.6 (CH_2), 22.2 (CH_3), 19.4 (CH_2).

Mixture of Diastereoisomers (A+B):

IR (neat) *v* (cm^{-1}) 3290, 2943, 2878, 2111, 1443, 1375, 1320, 1202, 1185, 1117, 1094, 1076, 1032, 983, 889, 873, 813.

HRMS (ESI+) calculated for $C_9H_{14}O_2Na$ $[M+Na]^+$: 177.0886, found: 177.0885.

4-((Tetrahydro-*2H*-pyran-2-yl)oxy)pent-2-yn-1-ol: (2.90)



$C_{10}H_{16}O_3$

To a stirred solution of alkyne **2.89** (diastereoisomer A; 8.0 g, 51.88 mmol) in dry THF (80 mL) at -78 ºC was added *n*-BuLi (2.3 M solution in hexanes, 23.68 mL, 54.47 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of powdered paraformaldehyde (3.11 g, 103.76 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched at 0 °C with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellowish liquid. The crude product **2.90** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.90** (7.93 g, 83%) as a pale yellow oil.

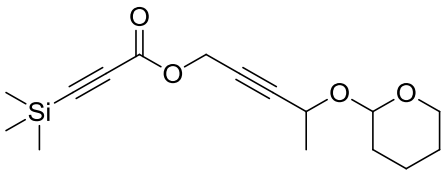
IR (neat) *v* (cm^{-1}) 3411, 2939, 2869, 1442, 1371, 1333, 1261, 1202, 1185, 1164, 1115, 1073, 1017, 998, 968, 932, 904, 872, 812.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.73 (t, *J* = 3.0 Hz, 1H), 4.44 (qt, *J* = 6.5, 1.5 Hz, 1H), 4.24 (dd, *J* = 6.0, 1.5 Hz, 2H), 3.98 – 3.90 (m, 1H), 3.52 – 3.47 (m, 1H), 1.84 – 1.44 (m, 6H), 1.37 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, CDCl3) δ 97.0 (CH), 85.9 (C), 82.5 (C), 62.6 (CH), 62.1 (CH_2), 50.7 (CH_2), 30.5 (CH_2), 25.2 (CH_2), 21.7 (CH_3), 19.0 (CH_2).

HRMS (ESI+) calculated for $C_{10}H_{16}O_3Na$ $[M+Na]^+$: 207.0991, found: 207.0986.

4-((Tetrahydro-*2H*-pyran-2-yl)oxy)pent-2-yn-1-yl 3-(trimethylsilyl)propiolate: (2.91)



$C_{16}H_{24}O_4Si$

To a stirred solution of 3-(trimethylsilyl)propiolic acid **2.65** (3.34 g, 23.52 mmol) and 4 drops of DMF in dry CH_2Cl_2 (40 mL) at 0 °C was added oxalyl chloride (3.13 g, 2.53 mL, 24.69 mmol). The solution was allowed to warm to rt and left to stir for 2 hours. This was added to a solution of propargylic alcohol **2.90** (6.50 g, 35.28 mmol) and 2,6-lutidine (7.56 g, 8.17 mL, 70.56 mmol) in dry CH_2Cl_2 (30 mL) which had been stirring for 30 minutes. The resultant cloudy solution was allowed to warm to rt and left to stir for 16 hours. The reaction mixture was then quenched with water. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.91** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.91** (5.95 g, 82%) as a yellow oil.

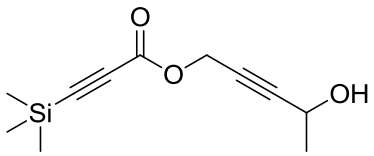
IR (neat) *v* (cm^{-1}) 2944, 2174, 1716, 1440, 1369, 1334, 1252, 1202, 1167, 1117, 1073, 1020, 982, 843, 761.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (d, *J* = 1.6 Hz, 2H), 4.71 (t, *J* = 3.3 Hz, 1H), 4.44 (q, *J* = 6.6 Hz, 1H), 3.95 – 3.88 (m, 1H), 3.51 – 3.45 (m, 1H), 1.85 – 1.45 (m, 6H), 1.38 (d, *J* = 6.7 Hz, 3H), 0.20 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.0 (C), 97.1 (CH), 95.1 (C), 93.8 (C), 88.4 (C), 76.7 (C), 62.3 (CH), 62.1 (CH_2), 53.5 (CH_2), 30.4 (CH_2), 25.3 (CH_2) 21.5 (CH_3), 19.0 (CH_2), -0.9 (CH_3).

HRMS (ESI+) calculated for $C_{16}H_{24}O_4SiNa$ $[M+Na]^+$ 331.1318, found 331.1322.

4-Hydroxypent-2-yn-1-yl 3-(trimethylsilyl)propiolate: (2.92)



$C_{11}H_{16}O_3Si$

To a stirred solution of tetrahydropyranyl ether **2.91** (1.90 g, 6.16 mmol) in methanol (10 mL) at 0 °C was added pyridinium *para*-toluenesulfonate (PPTS; 0.02 g). The reaction mixture was allowed to warm to rt and left to stir for 6 hours. The resultant solution was then quenched with saturated aqueous $NaHCO_3$ solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a dark yellow oil. The crude

product **2.92** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.92** (1.02 g, 78%) as a yellow oil.

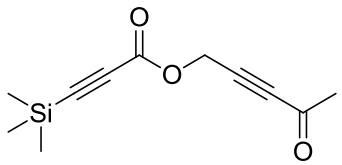
IR (neat) *v* (cm^{-1}) 3414, 2963, 2173, 1712, 1372, 1336, 1212, 1160, 1058, 1110, 1058, 1020, 953, 841, 759.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (d, *J* = 1.5 Hz, 2H), 4.55 (q, *J* = 6.6 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H), 0.23 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.1 (C), 95.5 (C), 93.7 (C), 89.4 (C), 76.8 (C), 58.1 (CH), 53.4 (CH_2), 23.8 (CH_3), -0.9 (CH_3).

HRMS (ESI) calculated for $C_{11}H_{16}O_3SiNa$ $[M+Na]^+$ 247.0887, found 247.0884.

4-Oxopent-2-yn-1-yl 3-(trimethylsilyl)propiolate: (2.87)



$C_{11}H_{14}O_3Si$

To a stirred solution of alcohol **2.92** (1.6 g, 7.13 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was added DMP (4.54 g, 10.69 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction mixture was then quenched with 10% aqueous $Na_2S_2O_3$ solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous K_2CO_3 solution, washed once with water, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude

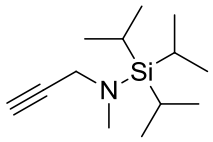
product **2.87** was purified by flash chromatography on a silica gel column eluting with 20% diethyl ether in hexanes to give the title compound **2.87** (1.31 g, 83%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (s, 2H), 2.35 (s, 3H), 0.26 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 183.2 (C), 151.6 (C), 96.5 (C), 93.2 (C), 85.8 (C), 83.4 (C), 52.4 (CH_2), 32.3 (CH_3), -1.0 (CH_3).

HRMS (ESI+) calculated for $C_{11}H_{14}O_3SiNa$ $[M+Na]^+$: 245.0685, found: 245.0683.

1,1,1-Triisopropyl-*N*-methyl-*N*-(prop-2-yn-1-yl)silanamine: (2.104)



$C_{13}H_{27}NSi$

To a stirred solution of *N*-methylpropargylamine **2.7** (5.0 g, 72.35 mmol) and triethylamine (10.97 g, 15.1 mL, 108.53 mmol) in dry CH_2Cl_2 (80 mL) at 0 °C was added neat triisopropylsilyl trifluoromethanesulfonate (23.28 g, 75.97 mmol). The resultant solution was allowed to warm to rt and left to stir for 16 hours. Subsequently the reaction mixture was quenched with water, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous K_2CO_3 solution, washed once with brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a pale yellow liquid. Distillation under reduced pressure afforded 15.49 g (96%) of clear colourless liquid.
Spectroscopic data are in agreement with the literature values.[144]

b.p.: 84 – 85 °C (1.6 Torr)

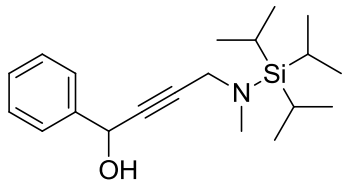
IR (neat) ν (cm^{-1}) 3311, 2944, 2865, 1463, 1142.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.58 (d, J = 2.1 Hz, 2H), 2.62 (s, 3H), 2.15 (t, J = 2.3 Hz, 1H), 1.20 – 1.11 (m, 3H), 1.07 (d, J = 7.0 Hz, 18H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 83.2 (C), 70.0 (CH), 40.6 (CH_2), 36.1 (CH_3), 18.2 (CH_3), 12.2 (CH).

HRMS (ESI+) calculated for $C_{13}H_{28}NSi$ $[M+H]^+$: 226.1986, found: 226.1982.

4-(Methyl(triisopropylsilyl)amino)-1-phenylbut-2-yn-1-ol: (2.105)



$C_{20}H_{33}NOSi$

To a stirred solution of alkyne **2.104** (10.0 g, 44.35 mmol) in dry THF (100 mL) at -78 ºC was added *n*-BuLi (2.5 M solution in hexanes, 18.62 mL, 46.57 mmol). The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of benzaldehyde (4.94 g, 4.75 mL 46.57 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched at 0 °C with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed twice with 10% aqueous K_2CO_3 solution, washed twice with 10% aqueous $NaSO_3H$ solution, washed once with water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellowish liquid. The crude product **2.105** was used directly in the next step without future purifications (14.12 g, 96%).

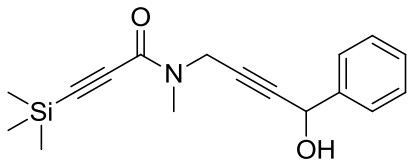
IR (neat) *v* (cm^{-1}) 3348, 2943, 2864, 1462, 1141, 1006.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 5.49 (s, 1H), 3.46 (d, *J* = 1.4 Hz, 2H), 2.46 (s, 3H), 2.25 (br s, 1H, OH), 1.21 – 1.10 (m, 3H), 1.10 – 1.02 (m, 18H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0 (C), 128.5 (CH), 128.2 (CH), 126.5 (CH), 84.3 (C), 83.6 (C), 64.4 (CH), 40.2 (CH_2), 35.2 (CH_3), 17.1 (CH_3), 12.0 (CH).

HRMS (ESI+) calculated for $C_{20}H_{34}NOSi$ $[M+H]^+$: 332.2391, found: 332.2404.

_N_-(4-Hydroxy-4-phenylbut-2-yn-1-yl)-_N_-methyl-3-(trimethylsilyl)propiolamide: (2.99)



$C_{17}H_{21}NO_2Si$

To a stirred solution of 4-(methyl(triisopropylsilyl)amino)-1-phenylbut-2-yn-1-ol **2.105** (7.7 g, 22.05 mmol) in MeCN (50 mL) in a PTFE container was added 40% aqueous HF (25 mL) in one portion *via* PTFE pipette. After stirring for 30 minutes, the reaction was quenched carefully with 10% aqueous K_2CO_3 solution. The aqueous phase was saturated with NaCl and extracted three times with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a brown liquid. The crude product **2.98** was used directly in the next step without future purifications (3.67 g, 95%).

To a stirred solution of 3-(trimethylsilyl)propiolic acid **2.65** (1.89 g, 13.32 mmol) and 4 drops of DMF in dry CH_2Cl_2 (20 mL) at 0 °C was added oxalyl chloride (1.77 g, 1.19 mL, 13.98 mmol). The solution was allowed to warm to rt and left to stir for 2 hours. This was added to

a solution of 4-(methylamino)-1-phenylbut-2-yn-1-ol **2.98** (3.5 g, 19.97 mmol) and 2,6-lutidine (4.23 g, 3.96 mL, 39.94 mmol) in dry CH_2Cl_2 (40 mL) which had been stirring for 30 minutes. The resultant cloudy solution was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched with water, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.99** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.99** (7.79 g, 80%) as a yellow oil.

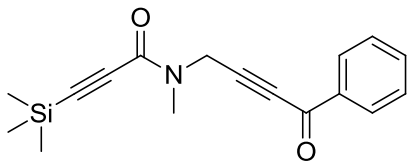
IR (neat) *v* (cm^{-1}) 3387, 2960, 2164, 1623, 1400, 1252, 1123.

^{1}H NMR (500 MHz, $CDCl_3$, resolved signals of rotamers) *Rotamer A*; δ 7.54 – 7.48 (m, 2H), 7.42 – 7.30 (m, 3H), 5.49 (d, *J* = 16.9 Hz, 1H), 4.33 (d, *J* = 3.2 Hz, 1.1H), 3.27 (s, 1.6H), 0.25 (dd, *J* = 5.0, 3.6 Hz, 9H); *Rotamer B*; δ 4.49 (d, *J* = 3.2 Hz, 0.9H), 3.02 (s, 1.4H),

^{13}C NMR (126 MHz, $CDCl_3$, Mixture of Rotamers A+B) δ 153.6 (C), 140.3 (C), 128.6 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 126.5 (CH), 126.5 (CH), 98.2 (C), 95.5 (C), 84.0 (C), 80.4 (C), 80.2 (C), 64.51 (CH), 40.9 (CH_2), 35.5 (CH_3), 35.5 (CH_2), 31.6 (CH_3), -0.7 (CH_3).

HRMS (ESI+) calculated for $C_{17}H_{21}NO_2SiNa$ $[M+Na]^+$: 322.1239, found: 322.1234.

_N_-Methyl-_N_-(4-oxo-4-phenylbut-2-yn-1-yl)-3-(trimethylsilyl)propiolamide: (2.94)



$C_{17}H_{19}NO_2Si$

Preparation of wet CH_2Cl_2:

H_2O (0.1 mL, 5.5 mmol) was solvated in 100 mL of CH_2Cl_2 by drawing the solvent mixture into and expelling it from a disposable pipet several times.

The wet CH_2Cl_2 (100 mL) was added slowly *via* the dropping funnel to a stirred solution of alcohol **2.99** (1.5 g, 5.0 mmol) and DMP (2.12 g, 5.0 mmol) in CH_2Cl_2 (30 mL). The clear solution grew cloudy towards the end of the wet CH_2Cl_2 addition, which required 30 minutes. The mixture was diluted with diethyl ether and then concentrated into a few mL of solvent by rotary evaporator. The residue was taken up in 100 mL of ether and then washed once with 10% aqueous $Na_2S_20_3$ solution, washed once with saturated aqueous $NaHC0_3$ solution, washed once with water and washed once with brine. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.94** was purified by flash chromatography on a silica gel column eluting with 15% diethyl ether in hexanes to give the title compound **2.94** (1.35 g, 91%) as a yellow oil.

IR (neat) *v* (cm^{-1}) 2962, 2917, 2232, 1711, 1639, 1396, 1259.

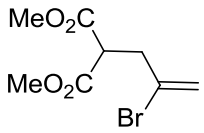
^1H NMR (500 MHz, $CDCl_3$, resolved signals of rotamers) *Rotamer A*; δ 8.11 (d, *J* = 7.3 Hz, 2H), 7.67 – 7.61 (m, 1H), 7.50 (td, *J* = 7.5, 3.7 Hz, 2H), 4.55 (s, 1.2H), 3.36 (s, 1.8H), 0.26 (d, *J* = 5.0 Hz, 9H); *Rotamer B*; δ 4.71 (s, 0.8H), 3.12 (s, 1.2H).

^{13}C NMR (126 MHz, $CDCl_3$, resolved signals of rotamers) *Rotamer A*; δ 177.3 (C), 153.7 (C), 136.3 (C), 134.3 (CH), 129.6 (CH), 128.6 (CH), 98.9 (C), 95.1 (C), 87.7 (C), 81.8 (C),

35.9 (CH_3), 35.6 (CH_2), -0.7 (CH_3); *Rotamer B*; δ 177.1 (C), 136.2 (C), 134.4 (CH), 129.5 (CH), 128.7 (CH), 99.0 (C), 95.0 (C), 87.3 (C), 82.4 (C), 41.0 (CH_2), 32.1 (CH_3).

HRMS (ESI+) calculated for $C_{17}H_{20}NO_2Si$ $[M+H]^+$: 298.1263, found: 298.12.

Dimethyl 2-(2-bromoallyl)malonate: (2.108)



$C_8H_{11}BrO_4$

To a stirred suspension of sodium hydride (60% *w/w* in mineral oil; 0.61 g, 15.14 mmol) in dry THF (40 mL) was added dimethyl malonate **2.107** (2.0 g, 15.14 mmol) in dry THF (15 mL). The resultant solution was cooled to 0 °C before the addition of 2,3-dibromo propene (3.02 g, 15.14 mmol). The reaction mixture was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.108** was purified by flash chromatography on a silica gel column eluting with 10% ethyl acetate in hexanes to give the title compound **2.108** (2.05 g, 54%) as a yellow oil.

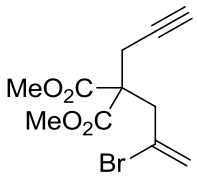
IR (neat) *v* (cm^{-1}) 2955, 2943, 2864, 1733, 1631, 1462, 1261, 1185, 1164, 1006, 968, 876.

^1H NMR (500 MHz, $CDCl_3$) δ 5.67 (d, *J* = 0.6 Hz, 1H), 5.46 (d, *J* = 1.6 Hz, 1H), 3.80 (t, *J* = 7.5 Hz, 1H), 3.73 (s, 6H), 3.00 (d, *J* = 7.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4 (C), 129.2 (C), 119.7 (CH_2), 52.6 (CH_3), 50.3 (CH), 40.4 (CH_2).

HRMS (ESI+) calculated for $C_8H_{11}BrO_4Na$ $[M+Na]^+$: 274.9733, found: 274.9741.

Dimethyl 2-(2-bromoallyl)-2-(prop-2-yn-1-yl)malonate: (2.109)



$C_{11}H_{13}BrO_4$

To a stirred suspension of sodium hydride (60% *w/w* in mineral oil; 0.16 g, 4.0 mmol) in dry THF (10 mL) was added dimethyl 2-(2-bromoallyl)malonate **2.108** (1.0 g, 4.0 mmol) in dry THF (10 mL). The resultant solution was cooled to 0 °C before the addition of propargyl bromide **2.49** (0.47 g, 0.3 mL, 4.0 mmol). The reaction mixture was then allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a pale yellow liquid. The crude product **2.109** was purified by flash chromatography on a silica gel column eluting with 5% diethyl ether in hexanes to give the title compound **2.109** (1.1 g, 96%) as a white solid.

m.p.: 40.5 - 41.5 °C

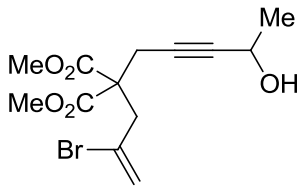
IR (neat) *v* (cm^{-1}) 3292, 2954, 2864, 1735, 1625, 1462, 1261, 1185, 1164, 1006, 968, 876.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (d, *J* = 0.5 Hz, 1H), 5.64 (d, *J* = 1.5 Hz, 1H), 3.77 (s, 6H), 3.32 (s, 2H), 2.94 (d, *J* = 2.6 Hz, 2H), 2.06 (t, *J* = 2.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4 (C), 126.1 (C), 122.8 (CH_2), 78.6 (C), 72.0 (CH), 55.9 (C), 53.0 (CH_3), 42.88 (CH_2), 22.24 (CH_2).

HRMS (ESI+) calculated for $C_{11}H_{13}BrO_4Na$ $[M+Na]^+$: 310.9889; found: 310.9874

Dimethyl 2-(2-bromoallyl)-2-(4-hydroxypent-2-yn-1-yl)malonate: (2.110)



$C_{13}H_{17}BrO_5$

To a stirred solution of alkyne **2.109** (0.5 g, 1.73 mmol) in dry THF (20 mL) at -78 ºC was added *n*-BuLi (2.5 M solution in hexanes, 0.73 mL, 1.82 mmol) The reaction was stirred 10 minutes at -78 °C and 15 minutes at -10 °C. The resultant solution was cooled to -78 °C before the addition of acetaldehyde (80 mg, 0.1 mL, 1.82 mmol). The reaction mixture was allowed to warm to rt and left to stir for 8 hours. The reaction was then quenched at 0 °C with cold water. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.110** was purified by flash chromatography on a silica gel column eluting with 30% diethyl ether in hexanes to give the title compound **2.110** (0.55 g, 96%) as a yellow oil.

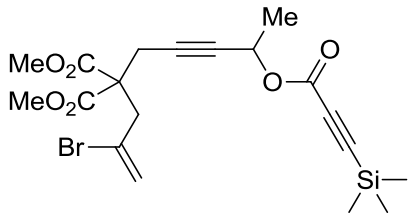
IR (neat) ν (cm^{-1}) 3428, 2984, 2958, 1731, 1626, 1435, 1371, 1325, 1291, 1253, 1202, 1145, 1068, 1002, 900, 850.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (d, *J* = 1.5 Hz, 1H), 5.62 (d, *J* = 1.5 Hz, 1H), 4.46 (qt, *J* = 6.5, 1.9 Hz, 1H), 3.75 (s, 6H), 3.29 (s, 2H) 2.96 (d, *J* = 1.9 Hz, 2H), 1.83 (br s, 1H), 1.45 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3 (C), 125.9 (C), 122.8 (CH_2), 86.9 (C), 78.6 (C), 58.3 (CH), 55.9 (C), 53.4 (CH_3) 42.5 (CH_2), 24.4 (CH_3), 22.7 (CH_2).

HRMS (ESI+) calculated for $C_{13}H_{17}BrO_5Na$ $[M+Na]^+$: 355.0152, found: 355.0153.

Dimethyl2-(2-bromoallyl)-2-(4-((3-(trimethylsilyl)propioloyl)oxy)pent-2-yn-1 ylmalonate: (2.111)



$C_{19}H_{25}BrO_6Si$

To a stirred solution of 3-(trimethylsilyl)propiolic acid **2.65** (0.2 g, 1.43 mmol) and 4 drops of DMF in dry CH_2Cl_2 (40 mL) at 0 °C was added oxalyl chloride (0.19 g, 0.12 mL, 1.5 mmol). The solution was allowed to warm to rt and left to stir for 2 hours. This was added to a solution of propargylic alcohol **2.110** (0.5 g, 1.5 mmol) and 2,6-lutidine (0.46 g, 0.49 mL, 4.29 mmol) in dry CH_2Cl_2 (20 mL) which had been stirring for 30 minutes. The resultant cloudy solution was allowed to warm to rt and left to stir for 16 hours. The reaction was then quenched with water, the phases were separated and the aqueous phase was extracted three

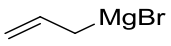
times with ethyl acetate. The organic layers were combined, washed once with 10% aqueous citric acid solution, washed once with 10% aqueous K_2CO_3 solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. The crude product **2.111** was purified by flash chromatography on a silica gel column eluting with 15% diethyl ether in hexanes to give the title compound **2.111** (0.65 g, 70%) as a yellow oil.

IR (neat) *v* (cm^{-1}) 2954, 2150, 1737, 1627, 1251, 1200.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (d, *J* = 1.5 Hz, 1H), 5.63 (d, *J* = 1.5 Hz, 1H), 4.47 (qt, *J* = 6.5, 1.7 Hz, 1H), 3.73 (s, 6H), 3.28 (s, 2H), 2.94 (d, *J* = 1.9 Hz, 2H), 1.37 (d, *J* = 6.5 Hz, 3H), 0.15 (s, 9H).

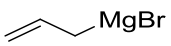
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5 (C), 169.4 (C), 126.3 (C), 122.6 (CH_2), 86,5 (C), 86.3 (C), 78.6 (C), 77.7 (C), 58.5 (CH), 56.0 (C), 52.9 (CH_3), 42.9 (CH_2), 25,7 (CH_3), 22.6 (CH_2), -0.07 (CH_3).

Allylmagnesium bromide (ethereal complex solution)



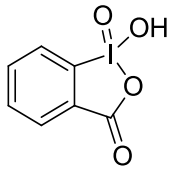
Prepared following the literature procedure.[220]

Allylmagnesium bromide (THF complex solution)



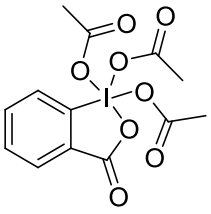
Prepared following the literature procedure.[220]

2-Iodoxybenzoic acid (IBX)



Prepared following the literature procedure.[221]

1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (DMP)



Prepared following the literature procedure.[221]

Chapter 5.
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